SYNTHETIC DESIGN AND BIOLOGICAL ACTIVITY OF NAAMIDINE A, RELATED NATURAL PRODUCTS AND ANALOGUES

by

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STATEMENT OF THESIS APPROVAL

The thesis of **Richard Amoafo Nkansah**

has been approved by the following supervisory committee members:

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ABSTRACT

This thesis describes the synthesis of several natural products, isolated from the marine sponges of the genus *Leucetta*, which have demonstrated an ability to influence a diverse range of biological processes, including the potential to inhibit important cancer signaling pathways. To understand this activity in more detail, the synthesis of naamidine A, related natural products and analogues was designed and implemented for the characterization of target binding *in vitro* and *in vivo*.

In addition, the expansion of synthetic application used towards these natural products is described. The resulting methodology was used for the synthesis of 2-thio and 2-oxoimidazoles.

TABLE OF CONTENTS

STANDARD LIST OF ABBREVIATIONS

Å	Ångström
Ac	acetyl
AcOH	acetic acid
AgOAc	silver acetate
Bn	benzyl
Boc	*tert*-butylcarbamate
BPS	*tert*-butyldiphenylsilyl
BSA	*N,O-bis* (trimethylsilyl)acetamide
n-Bu	butyl
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
t-BuLi	*tert*-butyllithium
°C	degrees Celsius
calcd	calculated
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
CI	chemical ionization
d	day(s); doublet (spectral)
DAST	diethylaminosulfur trifluoride

d.r.	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminun hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EDTA	ethylenediaminetetraacetic acid
EI	electron ionization
Et	ethyl
EtOH	ethanol
Et_2O	diethylether
EtOAc	ethyl acetate
Et_3N	triethylamine
g	gram(s)
GC	gas chromatography
h	hour(s)
HRMS	high-resolution mass spectrum
Hz	hertz
IC_{50}	50% inhibitory concentration
IR	infrared
J	coupling constant (in NMR)
K_2CO_3	potassium carbonate

KO*t*Bu	potassium *tert*-butoxide
La(OTf)	lanthanum trifluoromethanesulfonate
LDA	lithium diisopropyl amide
LRMS	low-resolution mass spectrum
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
M	molarity, mol/L; mega
Me	methyl
MeCN	acetonitrile
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
mL	milliliter
mol	mole(s)
MOM	methoxymethyl ether
mp	melting point
MS	mass spectrometry; molecular sieves
m/z	mass to charge ratio (in mass spectrometry)
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
$NaHSO_4$	sodiumhydrogen sulfate
Na_2SO_4	sodium sulfate
NBS	*N*-bromosuccinimide
NH_4Cl	ammonium chloride

NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million (in NMR)
*i*Pr	isopropyl
*i*Pr$_2$NH	diisopropylamine
*i*Pr$_2$NEt	diisopropylethylamine
py	pyridine
q	quartet (spectral)
quant	quantitative
R$_f$	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral); second(s)
t	triplet (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBS	tributylsilyl
Tf	trifluoromethanesulfonoyl, triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

TMS	trimethylsilyl, tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Trs	trisyl
Ts	*p*-toluenesulfonyl

ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Professor Ryan Looper, for his support and enthusiasm over the past few years. Professor Looper has been a tremendous inspiration to me. His seemingly endless knowledge of chemistry has inspired me to learn beyond the minimum as a scientist and his example as a professional role model has shaped my character. I owe him a great deal of gratitude for permitting me to work and study within his laboratory and I strongly believe that all of the work presented herein would not have been possible without his guidance and support.

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for a large audience and gave me the necessary foundation to present research in a clear and engaging manner. I would also like to acknowledge our post-doc Miao Yang, Travis Haussener, Anne Edwards and Hari Kanna Reddy for your encouragement and ability to keep the lab exciting on a daily basis. Finally, I would like to individually thank my lab mate Joe Gibbons. We entered the Looper group at the same time, probably with the same little understanding of what to expect. Working alongside Joe has been a fantastic experience and I am grateful for all the reasons listed above, but especially for his support and friendship. I believe that I have learned a great deal from him and I will miss working with a great chemist.

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and friend to me outside of chemistry. Working with her gave me the opportunity to contribute my knowledge of chemistry and a wealth of other skills I did not know I possessed to many student-athletes. Her attitude towards unconditional help and assistance is a trait that I will always strive to emulate.

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appreciate your encouragement and I am thrilled for the next chapter of our lives together.

CHAPTER 1

2-AMINOIMIDAZOLE NATURAL PRODUCTS

Introduction

Marine organisms are among the most promising sources for compounds with biological activity.[1] Natural products from the *Leucetta* genus of marine organisms have been isolated since the late 1980s and have been found to contain several related heterocyclic alkaloid scaffolds.[2] This family of alkaloids (Figure 1.1) is characterized by the presence of a 2-aminoimidazole moiety, which is substituted at various positions around the heterocycle and contains at least one benzylic fragment.[3] In a review published by Looper and coworkers,[4] it was suggested that the variations in the 2-aminoimidazole alkaloid skeleton could be roughly characterized into four categories related by successive biosynthetic condensation/oxidation reactions (Figure 1.1).

Several isolated 2-aminoimidazole natural products from each category have displayed a diverse range of biological activity. Naamine D (**1.1**), for example, was shown to be a modest competitive inhibitor of inducible nitric oxide synthase (iNOS), demonstrating a 50% reduction in nitric oxide production at 1.0 mM[5] (Figure 1.2). Kealiinine A (**1.3**) is shown to be toxic to brine shrimp (LD_{50} = 20 μg/mL), while Leucosolenamine A (**1.4**) is cytotoxic against the murine colon adenocarcinoma C-38

cell line. The *category II* 2-aminoimidazole naamidine A (**1.2**), in particular has served as a lead compound of interest for the Looper research group and has provided a sensible starting point for preliminary synthetic efforts and biological studies.

Naamidine A was isolated in 1987 from *Leucetta chagosensis*.[6] It was not until a decade later that biological studies correlated naamidine A with programmed cell death, or cellular apoptosis. Malfunctions of apoptosis are prevalent among several diseases including cancer, and so naamidine A has been increasingly viewed as a potential antitumor agent.[7] Initial studies by Ireland and co-workers showed that naamidine A was an inhibitor of the epidermal growth factor (EGF) receptor signaling, important in the development of some human tumors.[7] When tested in a mouse xenograft model, naamidine A inhibited tumor growth by 87% at a dose of 25 mg/kg. Naamidine A also lowered anti-mitogenic activity compared to similar *category II* natural products isonaamidine B (**1.5**) and isonaamidine C (**1.6**) (Figure 1.3) suggesting that naamidine A was selectively antagonizing the EGF signaling cascade. Ireland also showed that naamidine A was mildly cytotoxic towards the HCT116 human colon tumor cell line. Additional studies showed that an activator of the Ras-MAP kinase signaling pathway resulting in constant extracellular signal regulated kinases 1/2 (ERK1/2) activation leading to a G1 cell cycle arrest.[8] In 2009, Ireland later showed that naamidine A induces apoptosis by disruption of the mitochondrial membrane potential. This interruption leads to the activation of the pro-apoptotic factors caspases 3, 8 and 9.[9] The phenotypic response of naamidine A has garnered much attention for its antiproliferative effects on tumors. However, what has yet to be elucidated is the mechanism of action by which naamidine A induces these responses.

Previous Synthetic Strategies

The structural novelty of this highly substituted 2-aminoimidazole core and the biological activity associated with naamidine A have attracted synthetic interest. Interestingly, the current reported syntheses of naamidine A all employ unique strategies, yet rely on the synthesis of naamidine A's presumed biosynthetic precursor, naamine A.

Ohta's synthesis

Ohta has synthesized several members of the naamine and naamidine family.[10] In 2000, he began the synthesis of naamidine A with 1-methyl-2-phenylthio-1H-imidazole (**1.7**), and then sequentially functionalized the imidazole ring through a series of selective lithiation/addition reactions (Figure 1.4). Thiophenyl substituted imidazole **1.7** was first selectively lithiated with *t*-BuLi and followed by the addition of MOM protected *p*-hydroxybenzaldehyde to give alcohol **1.8.** The newly formed hydroxyl group was then protected as its TBS-ether. Next, bromination of the C-4 of the imidazole ring was accomplished to give **1.9**. A lithium-halogen exchange using *t*-BuLi was then followed by the addition of *p*-methoxybenzaldehyde to give tetrasubstituted imidazole **1.10** as an inconsequential 1:1 mixture of diastereomers. Desilylation of the TBS-ether with TBAF in THF gave diol **1.11**. Reduction of the thiophenol group with nickel (II) chloride/$NaBH_4$ gave **1.12** with a significant amount of the mono-deoxygenated products **1.13**. Deoxygenation of the carbinols with zinc powder in concentrated HCl/AcOH then gave the deprotected phenol, which subsequently was reprotected as its TBS-silyl ether to give **1.14**.

Selective bromination at the 2-position of the imidazole with NBS gave the

bromide which was followed by lithium/halogen exchange then addition to trisyl azide to give 2-azidoimidazole **1.15**. Hydrogenolysis of the azide yielded the 2-aminoimidazole. Deprotection of the phenolic TBS ether with TBAF gave the natural product naamine A (**1.16**). Conversion of **1.16** to naamidine A (**1.2**) was accomplished in 44% yield by the selective condensation of 1-methylparabanic acid in the presence of $TMSCl/Et_3N$. Overall, Ohta's synthesis of naamidine A required 13 linear steps with an overall yield of 1.2%.

Watson's synthesis

The second total synthesis of naamidine A was accomplished by Watson in 2006.[2] Watson began the synthesis of naamidine A with a selective N-methylation of the commercially available Boc protected amino acid **1.17** (Figure 1.5). Using conditions developed by Benoiton, Watson observed no methyl ester formation, forming exclusively the acid **1.18**. Methylation of the amine was essential to install the required regiochemistry in the ring. Formation of the Weinreb amide **1.19** was accomplished by *in situ* formation of the acid fluoride followed by the addition of *N,O*-dimethylhydroxyamine. Addition of magnesiated *p*-methoxybenzyl chloride gave the ketone **1.20**. Removal of the Boc group was accomplished using 4M HCl and the resulting suspension was then condensed with cyanamide to give the trisubstituted 2-aminoimidazole. Hydrogenolysis of the benzyl group gave naamine A (**1.16**). Installation of the dehydrohydantoin was accomplished using Otha's regioselective condensation procedure where 1-methyl-parabanic acid was first silylated with *N,O-bis* (trimethysilyl)acetamide (BSA), which was then reacted with **1.16** to give **1.2** in 80%

yield. Overall, Watson has improved the preparation of naamidine A from a fully protected tyrosine derivative in 8 linear steps and 20% overall yield.

First generation synthesis by Looper research group

While Ohta and Watson's syntheses of naamidine A offer direct access to the natural product, the synthetic design does not allow for expansion of the 2-aminoimidazole natural product catalogue. Within the Looper research group, a one-pot addition-hydroamination-isomerization sequence was envisioned to rapidly access the 2-aminoimidazole core of naamidine A not only to provide prompt access to naamidine A, but also to allow ease of functionalization for access to other *category I/II* alkaloid natural products and analogues (Figure 1.6).[11]

This work has led to studies conducted by Dr. Robert Giles towards the synthesis of naamidine A (Figure 1.7).[12] The propargyl cyanamides used in the study were constructed from a three-component iminium–acetylide addition (3-CC), which relied on stable precursors (an aldehyde, an amine, and an alkyne) to generate skeletal diversity. Beginning with alkyne **1.21**, the 3-CC conditions were employed forming propargyl amine **1.22**. The intermediate was then subjected to Von Braun conditions to yield propargyl cyanamide **1.23**. The addition of an amine to **1.23** generated the propargyl guanidine followed by the addition of the N–H bond across the tethered alkyne. Isomerization of the resultant intermediate formed the imidazole core for **1.24**. This strategy allowed for substitution on every position of the 2-aminoimidazole in only three steps and thus streamlined the preparation of the 2-aminoimidazole core. Following this was the deprotection of the piperidine ketal and hydrogenolysis to yield *category I*

natural product, naamine A (**1.16**). Subjecting **1.16** to similar silylating conditions reported by Watson afforded naamidine A (**1.2**). This convergent approach, completed in 2008, had provided the highest yielding synthesis of naamidine A (6 steps, 41% overall yield).

Interestingly, naamidine A and a number of *category II* alkaloids have been isolated as Zn^{2+} coordination complexes (Figure 1.8).[6] The first of these complexes, described by Fattorusso, was a homodimer of clathridine A. Further analysis of the X-ray crystal structure of **1.29** showed that the anionic clathridine acts as a bidentate ligand with dative bonding between both N-3 and N-8.[6]

Although the specific role of the *category II* alkaloid zinc dimers in nature are not fully understood, interesting research published by Hergenrother and coworkers[13] may offer clues to the unknown potential of these natural products. Hergenrother investigated the nature of caspase-3, a cysteine-aspartic acid protease essential for cellular apoptosis, catalyzing the hydrolysis of a multitude of protein substrates within the cell (Figure 8). The levels of procaspase-3 are typically high in cancer cells, suggesting that compounds that directly stimulate the activation of procaspase-3 to caspase-3 could selectively induce apoptosis in cells.[14] They reported that PAC-1 (**1.29**) and zinc form a tight complex with one another, suggesting that PAC-1 activates procaspase-3 *in vitro* by sequestering inhibitory zinc ions, thus allowing procaspase-3 to automatically activate itself to caspase-3 (Figure 1.9).

With knowledge of *category II* alkaloid affinity for zinc and the phenotypic similarities between PAC-1 and naamidine A, we suspect that naamidine A and other *category II* alkaloid natural products may operate in a mechanism similar to that of PAC-

1, for the initiation of cellular apoptosis by sequestering zinc. Exploring this theory with the naamidines and their related zinc dimers affords a sensible preliminary investigation for the mechanistic rationale of the *category II* alkaloid natural products.

Conclusion

Nature has exploited the 2-aminoimidazole as a natural product scaffold. Sponges of the genus *Leucetta* have provided an interesting class of highly substituted 2-aminoimidazoles having been shown to probe a diverse range of biological processes. Naamidine A has gathered prominent synthetic interest since it's preliminary biological evaluation. It is expected that the 2-aminoimidazole will provide an excellent scaffold for the preparation of high value small molecules for discovery based research and high throughput screening efforts.

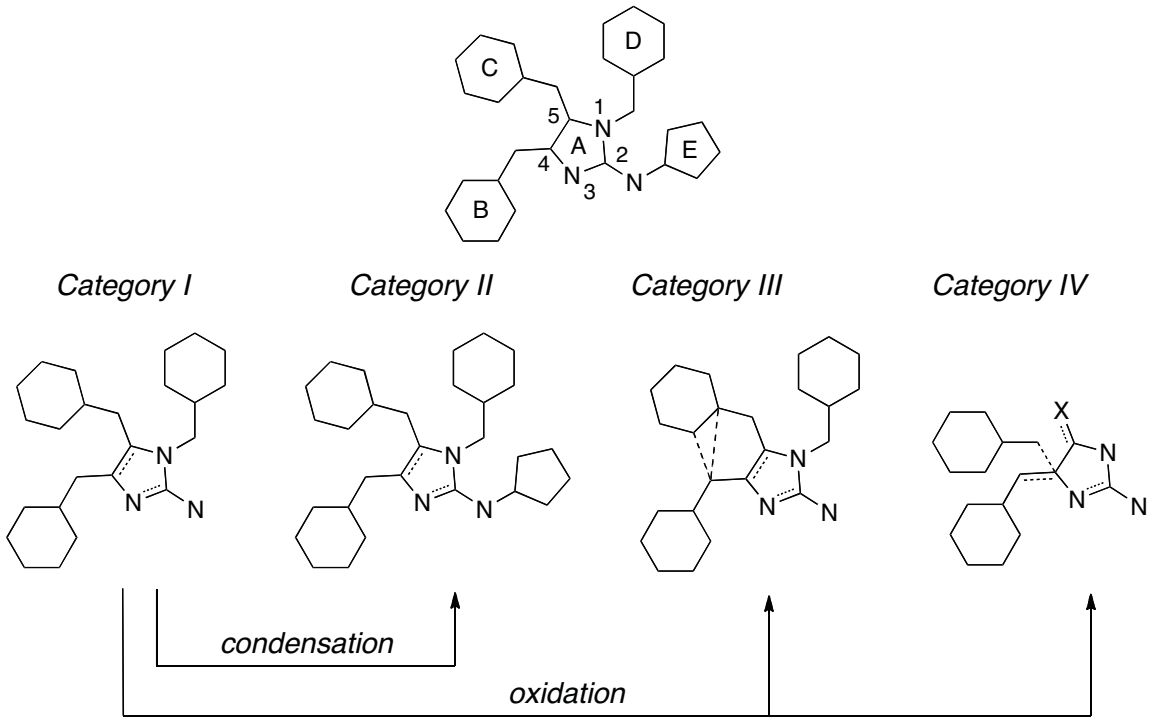
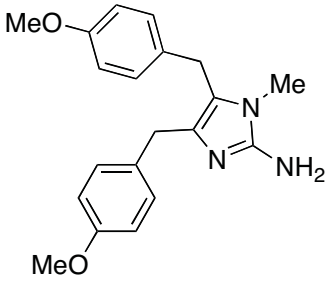


Figure 1.1. 2-aminoimidazole alkaloid skeletons

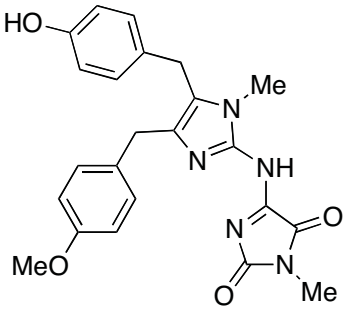
Category I



naamine D **1.1**
anti-fungal
C. neoformans
(MIC = 6.25 g/mL)

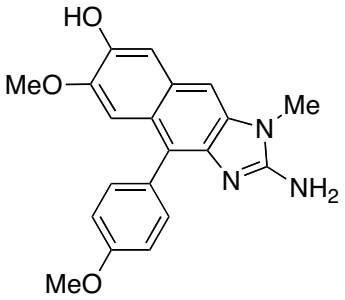
INOS Inhibitor
IC_{50} = 1.0 mM

Category II



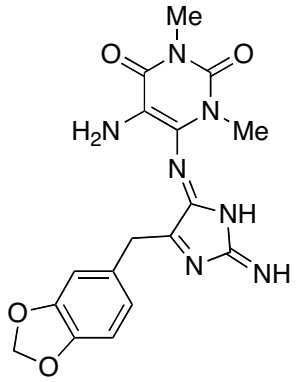
naamidine A **1.2**

Category IIi



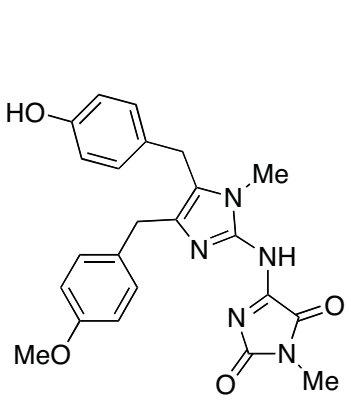
kealiinine A **1.3**
brine shrimp lethality
LD_{50} = 20 μg/mL

Category IV

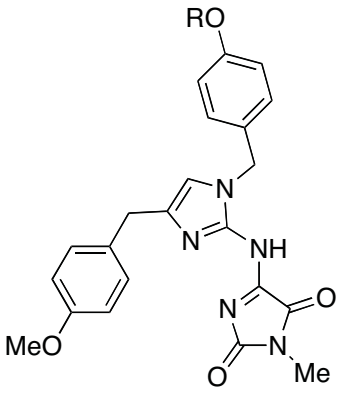


leucosolenamine A **1.4**
cytotoxic
C-38 colon adenocarcinoma

Figure 1.2. Selected examples of *category I-IV* 2-aminoimidazole natural products and their known biological activity.



naamidine A **1.2**



1.5, R = H; isonaamidine B
1.6, R = Me; isonaamidine C

	IC_{50} (μM)		
cell line	NIH3T3		HCT116
	EGF	insulin	cytotoxicity
1.2	11.3	242	72
1.5	22.7	9.8	1154
1.6	36.9	6.7	288

Figure 1.3. Naamidine A and the isonaamidines.

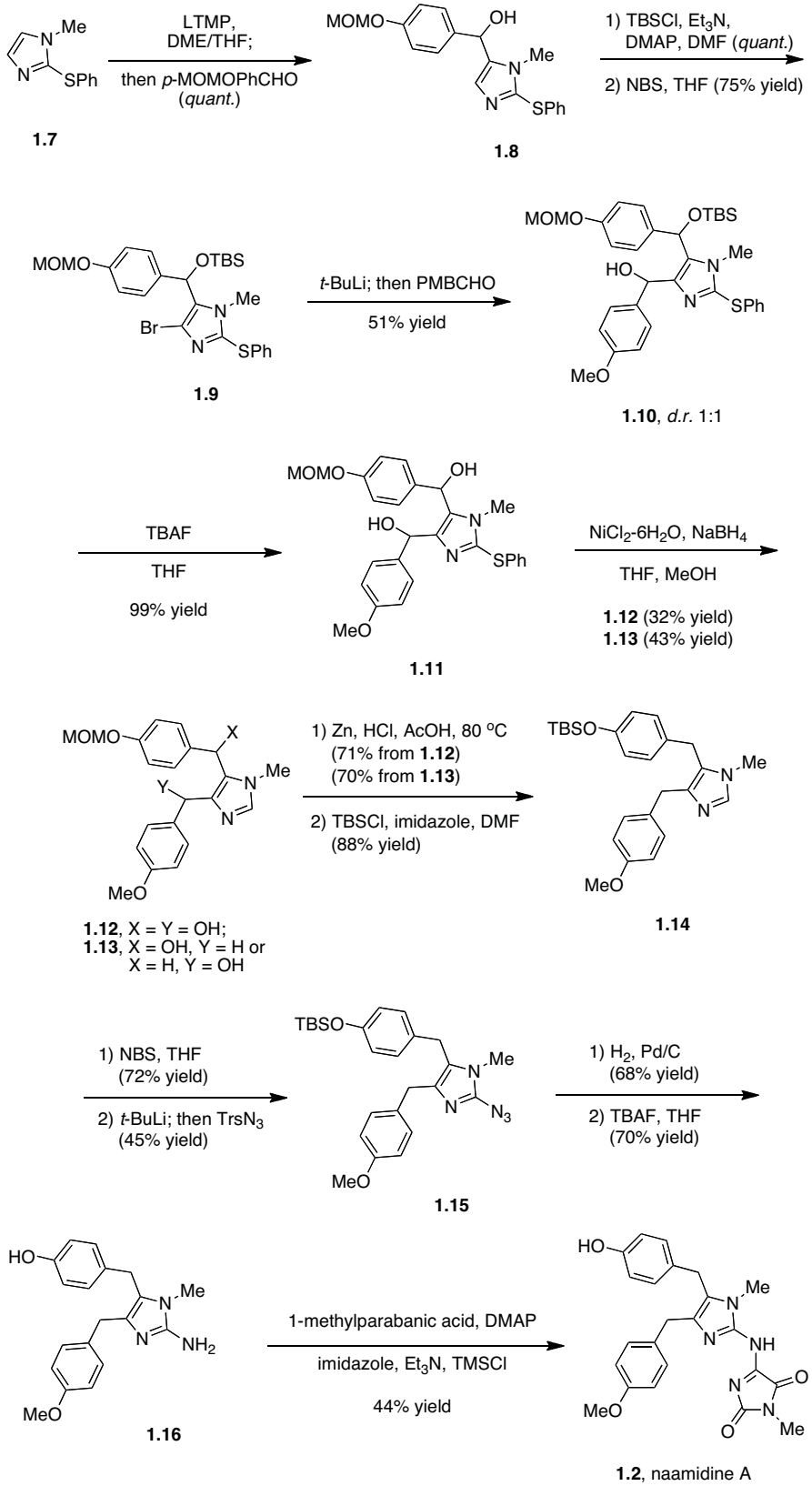
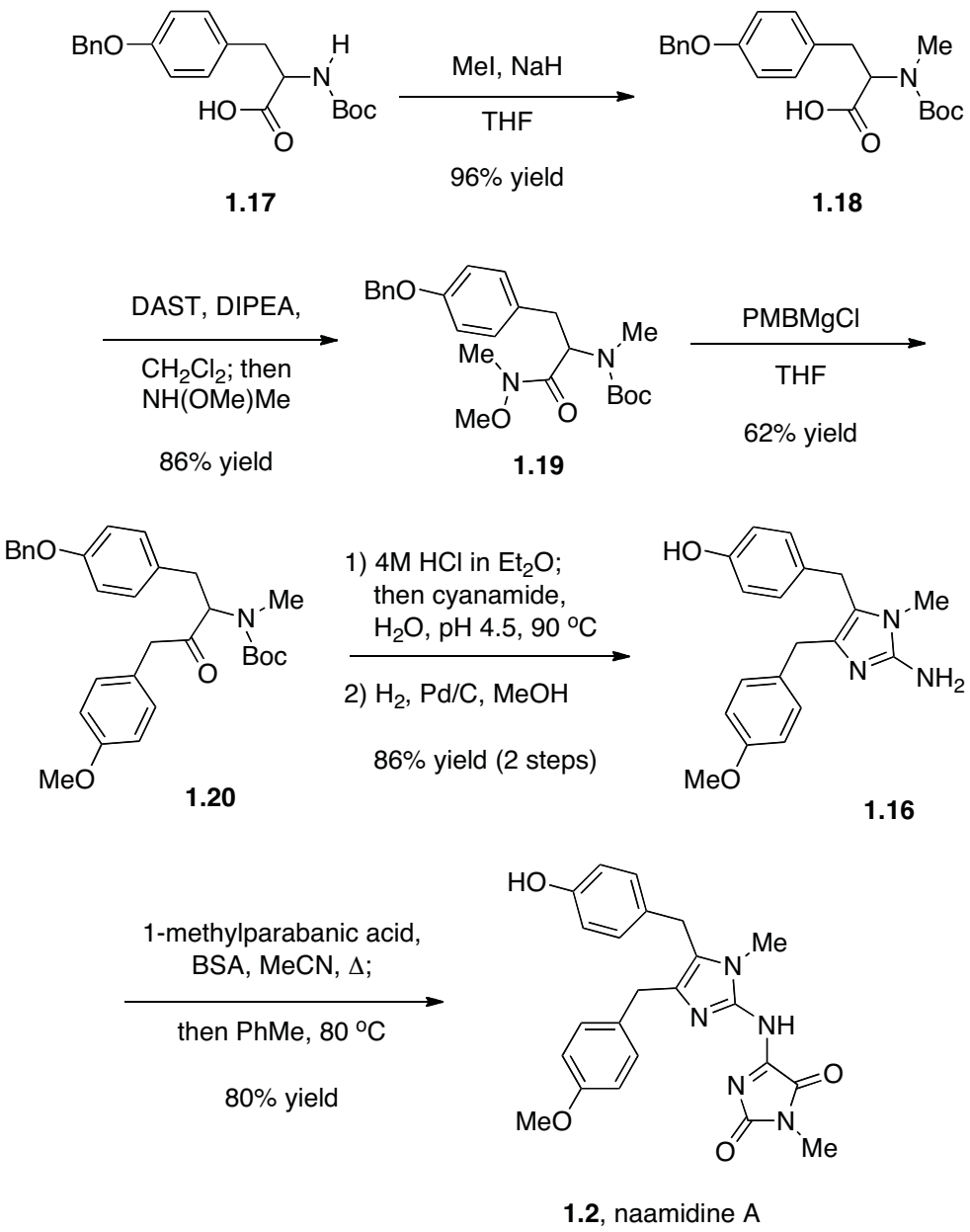


Figure 1.4. Ohta's synthesis of naamidine A.



1.17 **1.18** **1.19** **1.20** **1.16**

1.2, naamidine A

Figure 1.5. Watson's synthesis of naamidine A.

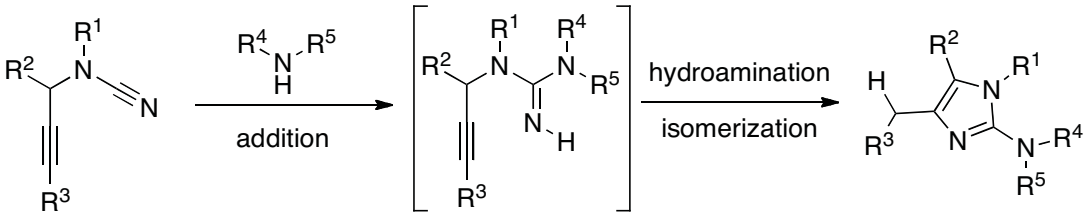


Figure 1.6. General approach to the 2-aminoimidazole core.

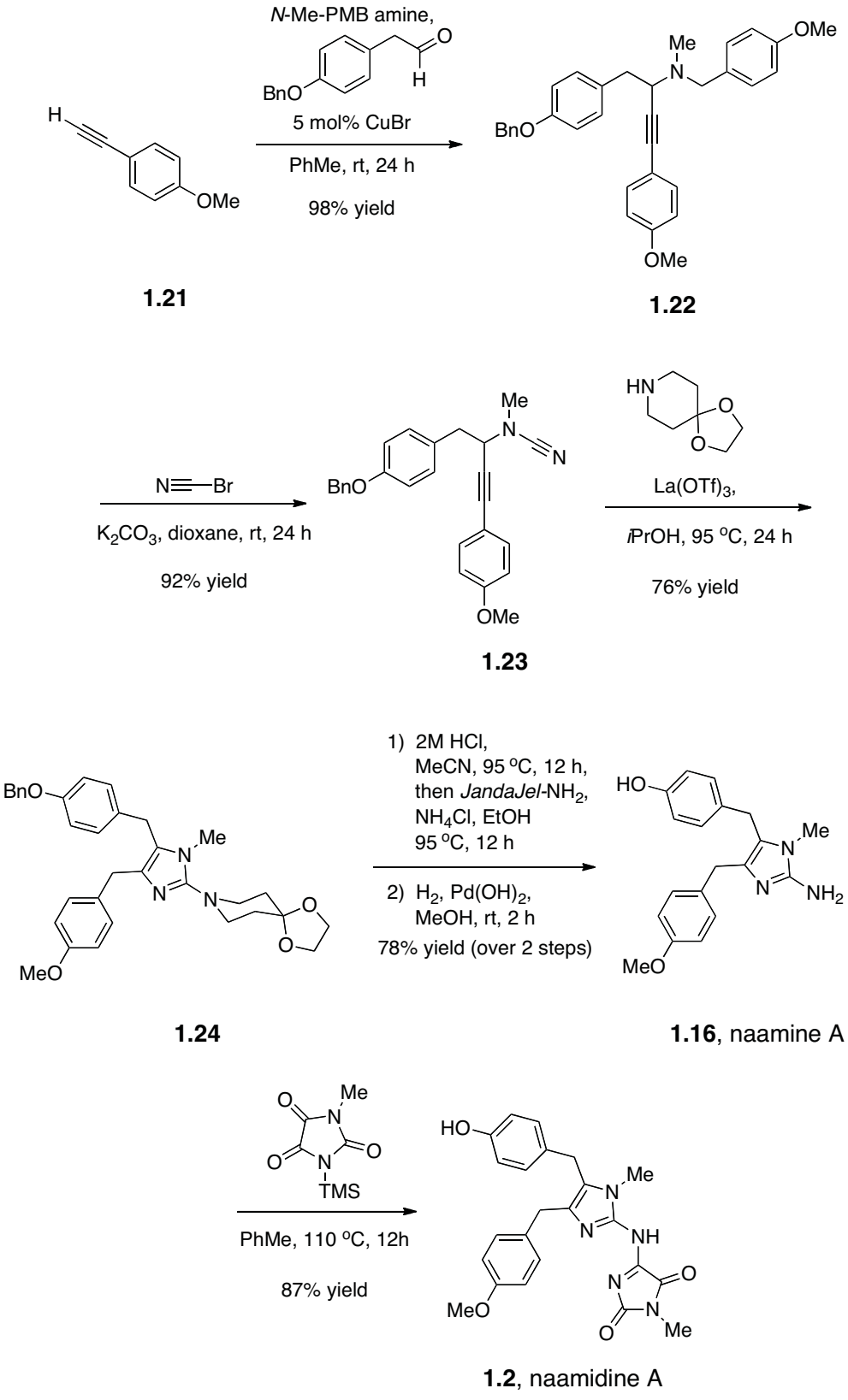
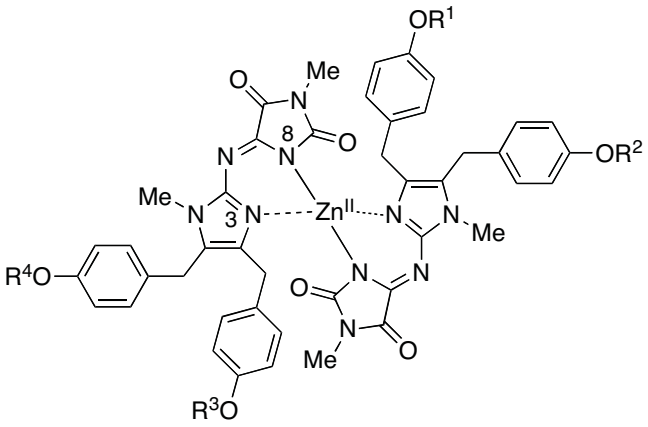
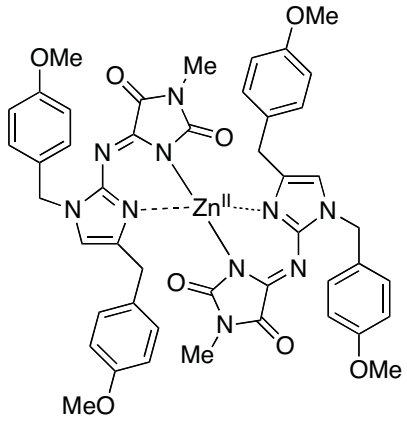


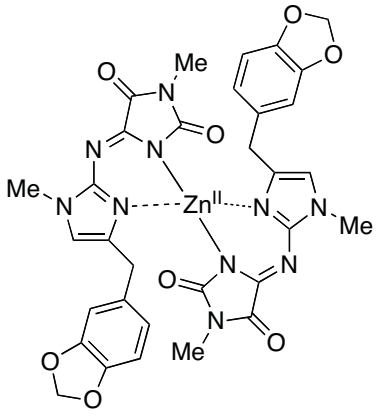
Figure 1.7. Looper first generation approach towards naamidine A.



1.25, R^1=R^3=Me; R^2=R^4=H (naamidine A+A)
1.26, R^1=R^2=R^3=R^4=Me (naamidine G+G)
1.27, R^1=R^2=R^3=Me; $R_4{}^4$=H (naamidine A+G)



1.28, (isonaamidine C)$_2$Zn



1.29, (clathridine A)$_2$Zn

Figure 1.8. Zinc complexes of *category II* alkaloids.

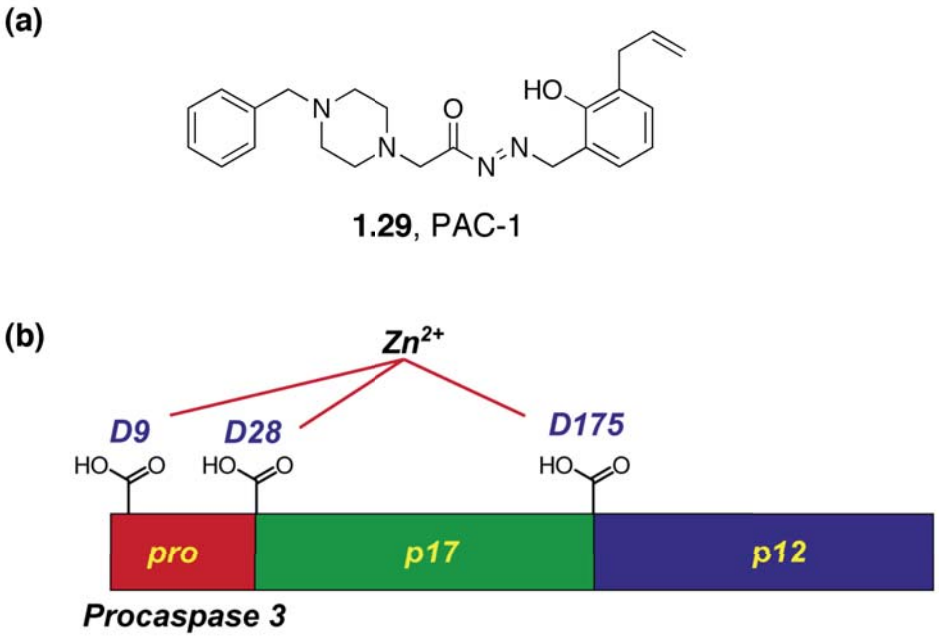


Figure 1.9. (a) Chemical Structure of PAC-1. (b) Procaspase 3 peptide domains D9, D28, D175 where proteolysis can occur.

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CHAPTER 2

SYNTHESIS OF NAAMIDINE A, RELATED NATURAL PRODUCTS AND ANALOGUES

Introduction

Based on the results from the preliminary investigation toward the synthesis of naamidine A and related natural products, modifications to the addition-hydroamination-cyclization chemistry were proposed in order to address limitations for accessing the 2-aminoimidazole core. Under these conditions the stereo-electronically favored 5-*exo*-dig cyclization was observed followed by isomerization. The major limitation of the methodology was that the addition of a nucleophile to the cyanamide was rate limiting and required forcing temperatures (>95 ^{o}C). However, the expense of adding piperidine-type nucleophiles and then removing their functionality to access the 2-aminoimidazole core resulted in variable reaction yields.

The improved synthetic design towards naamidine A was initially envisioned to utilize milder reaction conditions allowing the use of a preformed propargyl guanidine to access both *category I* and *II* natural products. Under the assumption that a π-Lewis acid might trigger the hydroamination process, a series of metal salts were evaluated by Looper and coworkers[1] for their ability to affect the regioselective cyclization of an intact

N,N-diBoc-propargylguanidine. In the end, it was determined that Ag(I) catalysts were optimum for the formation of the formal 5-*exo* dig product.

The improved synthetic approach (Figure 2.1) for access to the 2-aminoimidazole core now employed a secondary propargylamine (**2.3**) as the key intermediate still envisioned to come from established 3-CC procedures. With the ability to control the regioselective cyclization of the propargylguanidine with silver salts, access to the 2-aminoimidazole core can still be afforded by subsequent deprotection and condensation conditions to isolate the 2-aminoimidazole natural products, **2.1** and **2.2**, respectively.

Results and Discussion

Synthesis of naamidine A

The synthetic design for naamidine A began with the three-component coupling reaction (3-CC), which has been demonstrated for a number of substrates in high yields within the Looper research group[2] and was met with similar success in the isolation of propargylamine **2.5**, with all of the necessary functionality for what will become the 3-, 4- and 5-positions of the imidazole core (Figure 2.2). The propargyl amine was then subjected to mild acid-base reaction conditions for the generation of secondary amine **2.6**.

It was at this point where an efficient silver-catalyzed guanylation-cyclization reaction was employed. It was proposed that the addition of a diBoc-methylpseudothiourea to **2.6** in the presence of a weak base and metal catalyst would form a carbodiimide. This intermediate would react in a tandem guanylation-cyclization step to yield either the 5-*exo* dig (**2.7**) or 6-*endo* dig cyclized products. The addition of AgOAc with **2.6** afforded the 5-*exo* product in good selectivity and modest yield. The

regiomeric isomers could be successfully isolated, with the Boc-guanidine, **2.7**, carried forward to the desired natural product.

Naamidine A was ultimately obtained by the deprotection of the Boc groups and subsequent isomerization of **2.7** by treatment with acid to yield a *category I* type natural product, OBn-naamine A (**2.8**). With this intermediate now accessible, the addition of the hydantoin tail was achieved by reaction conditions first reported by Watson[3] for the synthesis of naamidine A. The addition of naamine to a silyl-imidazolidinetrione, afforded the benzyl-protected naamidine A (**2.9**). This was followed by the removal of the benzyl group functionality of **2.9** under standard hydrogenolysis conditions to yield naamidine A (**2.10**) in good yield (22% overall) and 6 total steps.

Expansion of category II natural products

It was thought that the layout for the synthesis of naamidine A could be applied to access several compounds containing the 2-aminoimidazole scaffold satisfying the characteristics of a *category II* natural product. This was first implemented with the selection of the required amine, alkyne and aldehyde building blocks for the copper mediated 3-CC. Several substrates were selected for the preparation of a series of propargylamines followed by the removal of the dimethoxybenzyl functionality upon treatment with TFAA, then NaOH for access to the secondary amine intermediates (**2.3a-e**). Not surprisingly, the robust reaction conditions offered a variety of intermediates in good yield. Amines **2.3a** and **2.3d** were envisioned as a key intermediates for the synthesis of clathridine A and isonaamidine A, respectively.

The resultant propargyl amines were then subjected to the silver catalyzed tandem guanylation-cyclization with excellent regiomeric selectivity for the 5-*exo* dig cyclic Boc-guanidine intermediates (**2.11a-e**, Figure 2.4). The cyclized Boc-guanidines were then treated with TFA to yield the isomerized *category I* 2-aminoimidazole intermediates (**2.2a-e**, Figure 2.5). It was initially proposed that this reaction could be coupled with the addition of TFA, where the deprotection of the Boc groups could be done *in situ* without the need for isolation and purification of **2.11a-e**. Unfortunately, the one-pot guanylation-cyclization-isomerization sequence was met with limited success, giving variable product yields across each secondary amine substrate. Thus, at the risk of marginalizing the overall yield of the reaction sequence, the guanylation and subsequent Boc group deprotection-isomerization conditions were kept as independent reaction sequences.

As anticipated, access to the *category II* natural products and analogues was achieved by the addition of **2.2a-e** to silylated *N*-methylparabanic acid to yield the *category II* type natural products and analogues (**2.1a-e**, Figure 2.6). The natural products, clathridine A (**2.1a**) and isonaamidine C (**2.1d**) were isolated as well as a series of three other analogues containing unique yet similar functional characteristics to other naamidine-like compounds as a method to probe any mechanistic overlap related to substitution around the heterocyclic core of the 2-aminoimidazole.

Zinc binding and isothermal titration calorimetry studies

With the initial isolation of clathridine A and its zinc homodimer, Fattorusso confirmed the presence of the zinc homodimer by the addition of $ZnSO_4$ in CH_2Cl_2 to

isolated clathridine A.[4] In an attempt to reproduce Fattorusso's early findings of clathridine A as its zinc homodimer, our synthetic product, **2.1a**, was treated with $ZnSO_4$ in solution of CH_2Cl_2 (Figure 2.7). The obtained ^1H NMR chemical shifts as well as mass spectral data proved to be consistent with Fattorusso's initial characterization.

As a measure for understanding the binding affinity of these *category II* natural product alkaloids, isothermal titration calorimetry was employed for a selection of prepared natural product alkaloids and analogues. This approach allowed determination of the binding constants of our compounds by directly measuring the heat evolved in liquid samples as a result of mixing precise amounts of reactants.

For this experiment, naamidine A as well as synthesized 2-aminoimidazole alkaloid natural products were prepared for calorimic titrations with the addition of a zinc (II) sulfate solution into a sample cell. Control experiments with standard zinc binding ligand EDTA were applied before any of the synthesized products were used to ensure that proper mixing and changes due to dilution for each sample was accounted for in the determination of the binding constants. The results of each calorimic titration are reported in Figure 2.9.

The most interesting feature of the titration data is the significant change in binding affinity between the clathridine products. The varied substitution of the aromatic ring in each of the products appears to play an important role in the strength of the N-3 and N-8 positions. The benzodioxole of clathridine A has created a stronger donating effect reducing the overall affinity of the molecule for zinc. Comparison of these results with naamidine A also appears to support the idea that the presence of either electron

withdrawing or donating groups on the rings of the 2-aminoimidazole core plays an important role in binding.

Conclusion

In summary, the synthetic design for access towards naamidine A offers immediate access to the *Leucetta* natural product catalogue in 6 steps with improved yields for further study into its biological activity. The binding studies of the naamidines and clathridines offer a point of reference for future experiements with the goal of confirming the mechanism of activity for naamidine A.

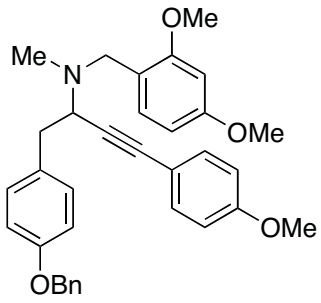
Experimental Section

General experimental procedures, materials and instrumentation

Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using flame-dried glassware. Triethylamine was distilled from CaH_2 immediately prior to use. Dichloromethane and toluene were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves.

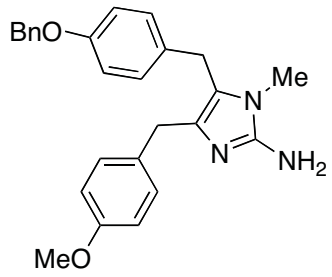
Yields were calculated for material judged by thin-layer chromatography and ^1H NMR. Thin-layer chromatography was performed on Merck Kieselgel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with either an ethanolic solution of 12-molybdophosphoric acid, *p*-anisaldehyde, or $KMnO_4$. Flash column chromatography was performed with Silicycle SiliaFlash® F60, slurry-

packed with solvents indicated in glass columns. ^{1}H NMR spectra were recorded on Varian Unity-300, Inova-400, or VXR-500 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances are reported relative to $CDCl_3$, DMSO-d_5, HOD, or HD_2COD using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), coupling constant(s) (*J* in Hz), integral]. 1,2 ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak[26] Infrared spectra were recorded on a Nicolet 380-FT IR spectrometer fitted with a SmartOrbit sample system. All absorptions are reported in cm^{-1} relative to polystyrene. Mass spectra were obtained at the University of Utah CIF on a Micromass Quattro II (ESI/APCI) for LRMS or an LCT XE premier (ESI/APCI-TOF) for HRMS. Isothermal titration calorimetry experiments were conducted using a MicroCal VP-ITC MicroCalorimeter fitted with Origin 7.0. UV-Vis experiments were recorded using a Beckman DU 650 Spectrophotometer.



1 - (4-(benzyloxy)phenyl) - N - (2,4 - dimethoxybenzyl) - 4 - (4 - methoxyphenyl) - N - methylbut-3-yn-2-amine 2.5. Prepared from the CuBr catalyzed 3-CC of 2-(4-(benzyloxy)phenyl)acetaldehyde, 1-(2,4-dimethoxyphenyl)-N-methylmethanamine, and 1-ethynyl-4-methoxybenzene to give propargylamine **2.5** (94% yield) as a dark red oil.

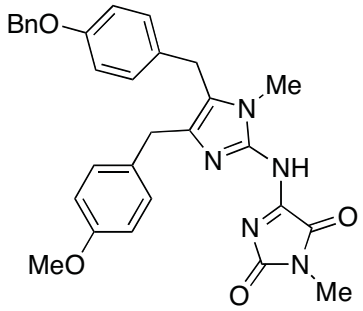
R_f = 0.30 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.41–7.35 (m, 5H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.45 (s, 1H), 6.42 (d, *J* = 8.3 Hz, 1H), 5.06 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.07–2.96 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.1, 159.5, 159.1, 157.6, 137.5, 133.3, 131.8, 131.4, 130.7, 128.8, 128.1, 127.7, 119.9, 116.0, 114.7, 114.0, 104.0, 98.8, 86.6, 85.9, 70.2, 59.1, 55.7, 55.6, 55.5, 52.6, 39.9, 38.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.7, 55.6, 55.5, 38.7; CH_2:, 70.2, 52.6, 39.9; CH_1: 133.3, 131.4, 130.7, 128.8, 128.1, 127.7, 114.7, 114.0, 104.0, 98.8, 59.1; CH_0: 160.1, 159.5, 159.1, 157.6, 137.5, 131.8, 119.9, 116.0, 86.6, 85.9; IR (neat) 2928, 2836, 1607, 1587, 1508, 1454, 1418, 1380, 1289, 1245, 1208, 1174, 1156, 1113, 1033, 919, 831, 737, 697 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{34}H_{36}NO_4$ (M+H) 522.2647, Obsd. 522.2644.



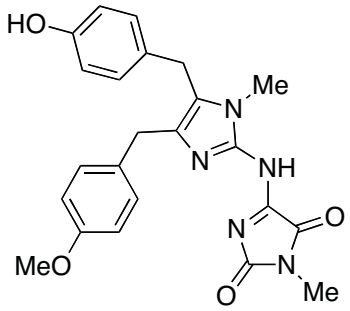
5-(4-(benzyloxy)benzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazol-2-amine 2.8.

Prepared to give **2.8** (88% yield) as a yellow oil. R_f = 0.30 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44–7.29 (m, 5H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.02 (s, 2H), 3.94 (bs, 2H), 3.81 (s, 2H), 3.75 (s, 5H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.9, 157.6, 147.1, 137.2, 133.5, 131.4, 129.7, 129.1, 128.8, 128.2, 127.7, 121.2, 115.1, 113.9, 70.2,

55.4, 32.7, 29.4, 28.9; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 29.4; CH_2: 70.2, 32.7, 28.9; CH_1: 129.7, 129.1, 128.8, 128.2, 127.7, 121.2, 115.1, 113.9; CH_0: 157.9, 157.6, 147.1, 137.2, 133.5, 133.3, 131.4, 121.2; IR (neat) 3381, 3109, 2909, 1644, 1611, 1552, 1510, 1248, 1174, 1030, 812, 737 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{26}H_{28}N_3O_2$ (M+H) 414.2182, Obsd. 414.2185.

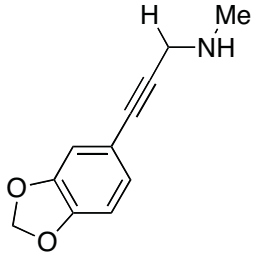


4-((5-(4-(benzyloxy)benzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazol-2-yl)amino)-1-methyl-1H-imidazole-2,5-dione 2.9. Prepared to give **2.9** (60% yield) as a yellow oil. R_f = 0.32 (50% EtOAc/hexanes); IR (neat) 2924, 2852, 1716, 1653, 1635, 1602, 1559, 1540, 1512, 1456, 1392, 1303, 1253, 1175, 1113, 1027, 834, 742 cm^{-1}



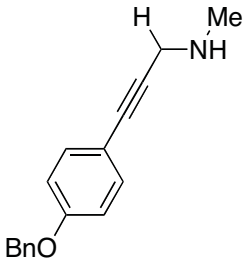
4-((5-(4-hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazol-2-yl)amino)-1-methyl-1H-imidazole-2,5-dione (Naamidine A) 2.10. Prepared according to general procedure F, to give **2.10** (82% yield) as a bright yellow solid. R_f = 0.30 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 3.89 (s, 4H), 3.78 (s,

3H), 3.47 (s, 3H), 3.17 (s, 3H); IR (neat) 2923, 2853, 2179, 2038, 1787, 1744, 1590, 1510, 1459, 1391, 1334, 1242, 1181, 1127, 1040, 1008 cm^{-1}

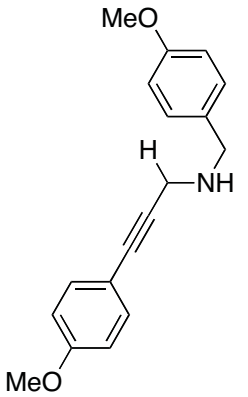


3-(benzo[d][1,3]dioxol-5-yl)-N-methylprop-2-yn-1-amine 2.3a. To a 250 mL round-bottomed flask containing a magnetic stir bar was added propargylamine (3.57 g, 10.53 mmol, 1.0 equiv.), triethylamine (2.93 mL, 21.05 mmol, 2.0 equiv.), and CH_2Cl_2 (100 mL). The reaction mixture was allowed to stir at -78 ^oC for 5 min as trifluoroacetic anhydride (2.95 mL, 21.05 mmol, 2.0 equiv.) was added to the flask and allowed to stir for an additional 20 min. 100 mL of water was added to the reaction and allowed to stir for 10 min. The organic portion of the reaction mixture was then isolated and solvent was removed under reduced pressure. The product was then taken up in MeOH and added to a 250 mL round-bottomed flask containing a magnetic stir bar and 4 M NaOH (18 mL). The reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was then concentrated under reduced pressure and taken up in CH_2Cl_2. The organic portion was washed with a solution of saturated NaCl and concentrated under reduced pressure to give the secondary amine product **2.3a** (1.67 g, 98% yield) as a clear oil. R_f = 0.28 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.90 (dd, *J* = 1.5, 7.8 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.92 (s, 2H), 3.54 (s, 2H), 2.48 (s, 3H), 1.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.9, 147.6, 126.3, 116.7, 112.0, 108.6, 101.5, 86.0, 83.5, 41.1, 35.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 35.7; CH_2:

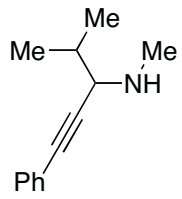
101.5, 41.1; CH_1: 126.3, 112.0, 108.6; CH_0: 147.9, 147.6, 116.7, 86.0, 83.5; IR (neat) 3335, 2892, 2789, 1603, 1502, 1485, 1438, 1327,1278, 1244, 1206, 1132, 1099, 1034, 969, 932, 878, 859, 807, 722, 695, 615, 542 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{11}H_{12}NO_2$ (M+H) 190.0876, Obsd. 190.0868.



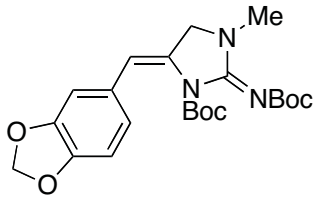
3-(4-(benzyloxy)phenyl)-N-methylprop-2-yn-1-amine 2.3b. Prepared to give the secondary amine **2.3b** (76 % yield) as a clear oil. R_f = 0.36 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38–7.29 (m, 7H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.02 (s, 2H), 3.55, (s, 2H), 2.49 (s, 3H), 1.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.7, 136.7, 133.2, 128.7, 128.2, 127.6, 115.8, 114.9, 86.3, 83.4, 70.1, 41.0, 35.6; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 35.6; CH_2: 70.1, 41.0; CH_1: 133.2, 128.7, 128.2, 127.6, 114.9; CH_0: 158.7, 136.7, 115.8, 86.3, 83.4; IR (neat) 3035, 2931, 2791, 1605, 1568, 1507, 1454, 1381, 1286, 1241, 1173, 1108, 1024, 831, 809, 737, 698, 599, 535 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{17}H_{18}NO$ (M+H) 252.1834 Obsd. 252.1388.



***N*,4-dimethyl-1-phenylpent-1-yn-3-amine 2.3d**. Prepared to yield the secondary amine **2.3d** (90% yield) as an orange oil. R_f = 0.29 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.35 (m, 2H), 7.33-7.27 (m, 2H), 6.86 (dddd, *J* = 18.0, 8.0, 5.0, 5.0 Hz, 4H), 3.88 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H) 3.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 133.2, 132.3, 132.2, 132.1, 132.0, 129.8, 128.7, 128.6, 114.1, 114.0, 113.9, 55.4, 52.0, 38.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4; CH_2: 52.0, 38.2; CH_1: 133.2, 132.1, 129.8, 128.7, 114.1; CH_0: 132.3, 132.1, 132.0, 128.6, 114.0, 113.9; IR (neat) 2932, 2835, 1606, 1510, 1463, 1439, 1291, 1248, 1174, 1119, 1032, 833, 750, 721, 696, 541 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{18}H_{20}NO_2$ (M+H) 282.1497, Obsd. 282.1494.

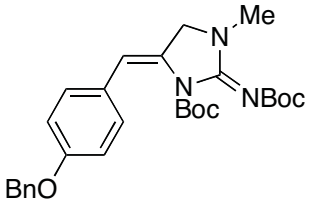


***N*,A-dimethyl-1-phenylpent-1-yn-3-amine 2.3e**. Prepared to give secondary propargylamine **2.3e** (91% yield) as a yellow oil. R_f = 0.45 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45–7.41 (m, 2H), 7.33–7.30 (m, 3H), 3.25 (d, *J* = 5.7 Hz, 2H), 2.57 (s, 3H), 1.95, (app d7, *J* = 6.6, 10.3 Hz, 1H), 1.78 (s, 1H), 1.07 (t, *J* = 4.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8, 128.7, 128.0, 114.1, 89.4, 84.8, 59.1, 55.4, 34.7, 32.8, 19.9, 18.0; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 34.7, 19.9, 18.0; CH_1: 131.8, 128.7 128.3, 128.0, 114.1, 59.1, 32.8; CH_0: 89.4, 84.8, 55.4; IR (neat) 2959, 2870, 2794, 2361, 2339, 1598, 1512, 1489, 1467, 1442, 1384, 1366, 1343, 1323, 1300, 1246, 1171, 1131, 1105, 1070, 1029, 914, 817, 755, 691, 668 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{13}H_{18}N$ (M+H) 188.1438, Obsd. 188.1439.

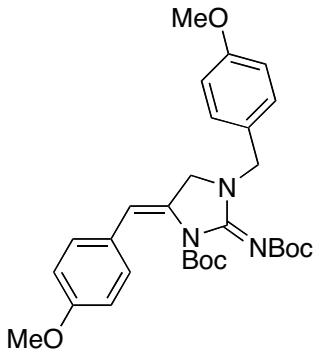


(5Z) - *tert* - butyl - 5 - (benzo[d][1,3]dioxol - 5 - ylmethylene) - 2-((*tert* - butoxycarbonyl)imino)-3-methylimidazolidine-1-carboxylate 2.11a. To a 25 mL round-bottomed flask containing a magnetic stir bar was added secondary propargylamine (0.437 g, 2.31 mmol, 1.0 equiv.), 1,3-Bis(*tert*-butoxycarbonyl)-2-methyl-2-pseudothiourea (0.677 g, 2.31 mmol, 1.0 equiv.), AgOAc (0.578 g, 3.47 mmol, 1.5 equiv.), triethylamine (1.7 mL, 11.55 mmol, 5.0 equiv.), and CH_2Cl_2 (24 mL). The reaction mixture was allowed to stir under N_2 at rt for 24 h. The reaction mixture was filtered through a plug of celite before the solvent was removed under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 5.7 × 15 cm column, eluting with 200 mL 50% EtOAc/hexanes, 200 mL 70% EtOAc/hexanes, then 90% EtOAc/hexanes. The product containing fractions were combined and then concentrated under reduced pressure to give the 5-*exo*-dig imidazole **2.11a** (0.699 g, 70% yield) as a light brown oil. R_f = 0.33 (90% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 1.5, 8.3 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 2H), 5.85 (s, 1H), 3.96 (d, *J* = 1.5 Hz, 2H), 2.96 (s, 2H), 1.52 (s, 9H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4, 152.0, 148.6, 147.7, 146.9, 130.1, 127.9, 123.0, 116.0, 109.1, 108.2, 101.2, 83.6, 79.5, 52.8, 31.8, 27.5, 27.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 31.8, 27.5, 27.7; CH_2: 101.2, 52.8; CH_1: 123.0, 116.0, 109.1, 108.2; CH_0: 159.4, 152.0, 148.6, 147.7, 146.9, 130.1, 127.9, 83.6, 79.5 ; IR (neat) 2977, 2931, 1746, 1711, 1683, 1638, 1503, 1488, 1444, 1391, 1367, 1294,

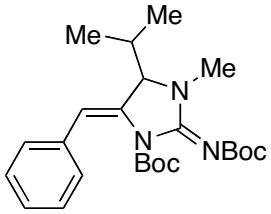
1254, 1236, 1150, 1060, 1037, 956, 929, 872, 846, 795, 768, 733, 667 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{22}H_{30}N_3O_6$ (M+H) 432.2146, Obsd. 432.2135.



(5Z)-tert-butyl-5-(4-(benzyloxy)benzylidene)-2-((tert-butoxycarbonyl)imino)-3-methylimidazolidine-1-carboxylate 2.11b. Prepared to give **2.11b** (75% yield) as a light brown oil. R_f = 0.29 (50% EtOAc/hexanes ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, *J* = 6.8 Hz, 2H), 7.36 (t, J = 7.3 Hz, 3H), 7.33–7.31 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.92 (s, 1H), 5.09 (s, 2H), 4.00 (d, *J* = 2.0 Hz, 2H), 3.00 (s, 3H), 1.56 (s, 9H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 157.8, 152.1, 148.5, 137.0, 130.1, 128.9, 128.7, 128.0, 127.5, 115.7, 114.7, 83.4, 79.1, 70.0, 52.7, 31.7, 28.3, 27.4; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 31.7, 28.3, 27.4; CH_2: 70.0, 52.7; CH_1: 130.1, 128.7, 128.0, 127.5, 115.7, 114.7, 77.5; CH_0: 159.5, 157.8, 152.1, 148.5, 137.0, 128.9, 127.5, 83.4, 79.1; IR (neat) 2977, 2927, 1745, 1711, 1688, 1679, 1631, 1607, 1511, 1468, 1453, 1367, 1299, 1245, 1175, 1148, 1024, 847, 743, 697 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{28}H_{36}N_3O_5$ (M+H) 494.2657, Obsd. 494.2655.

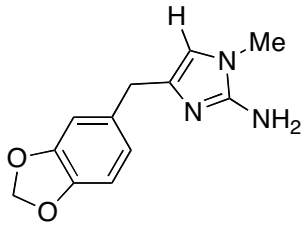


(5Z) - *tert* – butyl - 5 – benzylidene - 2 - ((*tert* - butoxycarbonyl)imino) - 4 - isopropyl - 3-methylimidazolidine-1-carboxylate 2.11d. Prepared to give **2.11d** (72% yield) as a light yellow oil. R_f = 0.30 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.84 (s, 1H), 4.57 (s, 2H), 3.81 (s, 3H), 3.80 (s, 2H), 3.79 (s, 3H), 1.59 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.7, 159.5, 159.4, 152.1, 148.6, 130.1, 130.0, 128.7, 127.5, 127.4, 115.9, 114.2, 113.6, 83.5, 79.3, 55.4, 55.3, 49.6, 47.9, 28.3, 27.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.3, 28.3, 27.5; CH_2: 49.6, 47.9; CH_1: 130.1, 130.0, 115.9, 114.2, 113.6; CH_0: 159.7, 159.5, 159.4, 152.1, 148.6, 128.7, 127.5, 127.4, 83.5, 79.3; IR (neat) 2918, 2849, 2362, 2339, 2228, 2168, 2158, 2141, 2118, 1745, 1684, 1634, 1610, 1513, 1457, 1393, 1367, 1301, 1249, 1175, 1151, 1123, 1033, 851, 767, 668, 568, 540 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{29}H_{38}N_3O_6$ (M+H) 524.2769, Obsd. 524.2761.



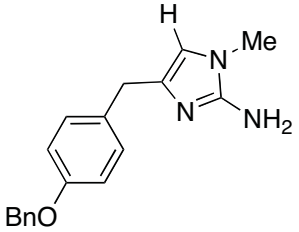
(5Z) - tert - butyl - 5 - benzylidene - 2 - ((tert - butoxycarbonyl)imino) - 4 - isopropyl-3-methylimidazolidine-1-carboxylate 2.11e. Prepared to give **2.11e** (71% yield) as a light yellow oil. R_f = 0.29 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (s, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.26–7.15 (m, 5H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.88 (s, 1H), 4.68 (dd, *J* = 12.2, 257.3 Hz, 1H), 3.78 (s, 1H) 3.75 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.8, 159.6, 152.6, 148.0, 136.1, 136.0, 131.9, 130.8, 130.2, 128.8, 128.4, 128.2, 127.6, 127.2, 127.0,

117.8, 113.7, 112.8, 83.1, 79.2, 68.5, 66.4, 55.3, 31.3, 31.0, 30.8, 29.2, 28.4, 27.3, 18.2, 17.6, 16.0, 15.8; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.3, 31.3, 30.8, 29.2, 28.4, 27.3, 18.2, 17.6, 16.0, 15.8; CH_1: 130.2, 128.8, 128.4, 128.2, 127.6, 127.2, 127.0, 117.8, 113.7, 112.8, 68.5, 66.4, 31.0; CH_0: 159.8, 159.6, 152.6, 148.0, 136.1, 136.0, 131.9, 130.8, 83.1, 79.2; IR (neat) 2964, 2931, 1782, 1746, 1710, 1681, 1634, 1515, 1449, 1388, 1366, 1296, 1234, 1169, 1146, 1060, 973, 921, 852, 800, 771, 730, 697, 668, 602 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{24}H_{36}N_3O_4$ (M+H) 430.2708, Obsd. 430.2706.

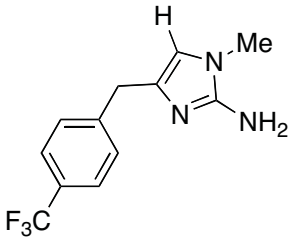


(4-(benzo[d][1,3]dioxol-5-ylmethyl)-1-methyl-1H-imidazol-2-amine) 2.2a. To a 50 mL round-bottomed flask containing a magnetic stirbar was added imidazole **2.11a** (0.15 g, 0.36 mmol, 1.0 equiv.), trifluoroacetic acid (1.4 mL, 18.03 mmol, 50 equiv.), and CH_2Cl_2 (4 mL). The reaction mixture was allowed to stir at reflux for 1.5 h. The solution was washed with 2M NaOH (20 mL) and the organic layer was dried over $NaSO_4$ and concentrated under reduced pressure to give **2.2a,** (0.081 g, 91% yield) as a yellow oil. R_f = 0.33 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.71 (s, 1H), 6.67 (d, *J* = 1.0 Hz, 2H), 6.08 (s, 1H), 5.86 (s, 2H), 3.62 (s, 2H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.7, 146.0, 137.3, 134.4, 121.8, 113.2, 109.6, 108.3, 101.0, 34.8, 31.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 31.5; CH_2: 101.0, 34.8; CH_1: 121.8, 113.2, 109.6, 108.3; CH_0: 147.7, 146.0, 137.3, 134.4; IR (neat) 3117, 2900, 1671, 1631, 1547, 1501, 1488, 1442, 1344, 1243, 1186, 1120, 1096, 1037, 927, 864, 809,

775, 713, 660 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{12}H_{14}N_3O_2$ (M+H) 232.1094, Obsd. 232.1086.

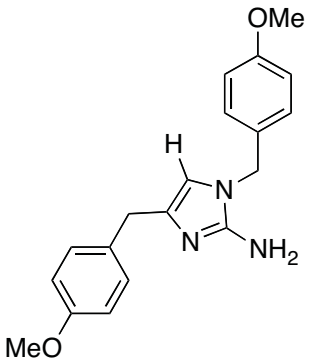


4-(4-(benzyloxy)benzyl)-1-methyl-1H-imidazol-2-amine 2.2b. Prepared to give **2.2b,** (70% yield) as a light yellow oil. R_f = 0.45 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38–7.25 (m, 5H), 7.12 (d, *J* = 8.3 Hz), 6.85 (d, *J* = 8.3 Hz), 5.95 (s, 1H), 4.98 (s, 2H), 3.64 (s, 2H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.4, 147.8, 137.3, 135.6, 132.2, 129.9, 128.7, 128.0, 127.6, 114.9, 112.8, 70.1, 33.4, 31.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 70.1, 31.5; CH_2: 33.4; CH_1: 129.9, 128.7, 128.0, 127.6, 114.9, 112.8; CH_0: 157.4, 147.8, 137.3, 135.6, 132.2; IR (neat) 3033, 2927, 2869, 1722, 1642, 1601, 1508, 1454, 1405, 1381, 1342, 1289, 1245, 1172, 1135, 1077, 1024, 913, 832, 793, 739, 697, 617 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{18}H_{20}N_3O$ (M+H) 294.1607 Obsd. 294.1606.

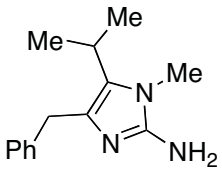


1-methyl-4-(4-(trifluoromethyl)benzyl)-1*H*-imidazol-2-amine 2.2c. Prepared to give **2.2c** (97% yield) as a yellow oil. R_f = 0.27 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.02 (s, 1H), 3.87 (s, 2H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.9, 132.4, 129.3, 126.0, 112.6, 38.7,

31.8, 31.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 31.8; CH_2: 31.2; CH_1: 129.3, 126.0, 112.6; CH_0: 147.9, 132.4, 38.7; IR (neat) 3140, 2924, 2177, 1674, 1547, 1422, 1326, 1203, 1174, 1126, 1067, 1019, 837, 799, 722, 597 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{12}H_{13}F_3N_3$ (M+H) 256.1062, Obsd. 256.1062.

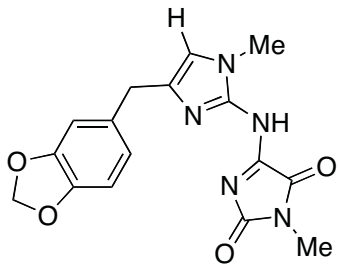


4-benzyl-5-isopropyl-1-methyl-1H-imidazol-2-amine 2.2d. Prepared to give **2.2d** (35% yield) as a light yellow oil. R_f = 0.20 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5, 2H), 6.86 (d, *J* = 8.5, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.14 (s, 1H), 4.74 (s, 2H), 3.93 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.7, 158.2, 147.6, 137.6, 132.5, 130.1, 128.6, 128.3, 114.7, 114.1, 112.8, 55.7, 55.6, 48.5, 34.3 ; IR (neat) 3345, 2934, 2838, 1739, 1666, 1610, 1513, 1453, 1392, 1302, 1249, 1177, 1031, 835, 756, 610, 562 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{19}H_{22}N_3O_2$ (M+H) 324.1702, Obsd. 324.1712**.**



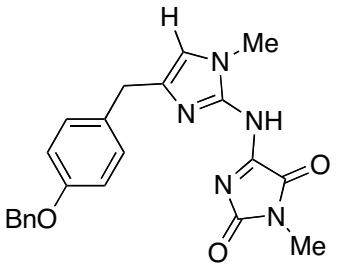
4-benzyl-5-isopropyl-1-methyl-1H-imidazol-2-amine 2.2e. Prepared to give **2.2e** (88% yield) as a light yellow oil. R_f = 0.10 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29–7.18 (m, 5H), 3.83 (s, 2H), 3.39 (s, 3H), 2.97 (dq, 1H), 1.27 (s, 3H), 1.25

(s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.0, 137.7, 128.9, 128.3, 127.5, 126.9, 120.5, 30.6, 29.8, 24.5, 21.3; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 29.8, 21.3; CH_2: 30.6; CH_1: 24.5; CH_0: 147.0, 137.7, 127.5, 120.5; IR (neat) 3136, 2968, 2925, 2361, 2338, 1734, 1669, 1635, 1558ha

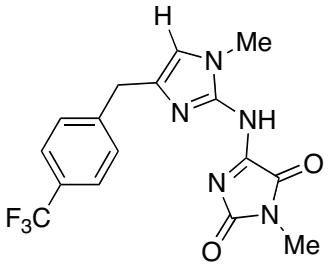


Clathridine A (4-((4-(benzo[d][1,3]dioxol-5-ylmethyl)-1-methyl-1H-imidazol-2-yl)amino)-1-methyl-1H-imidazole-2,5-dione) 2.1a. 1-methylparabanic acid (0.361 g, 2.80 mmol, 8 equiv.) in MeCN (2.5 mL) was treated with *N,O*-bis(trimethylsilyl)acetamide (857 μL, 3.50 mmol, 10 equiv.) and stirred at reflux for 1 h. The yellow solution was concentrated to dryness under vacuum, opened to dry N_2 to minimize exposure to air of the silylated product. The residue was taken in toluene (3.5 mL) and added to **2.2a** (0.081 g, 0.35 mmol, 1.0 equiv). The mixture was stirred overnight at reflux then diluted with EtOAc (25 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated to dryness. Purification of the material was accomplished by flash column chromatography on a 5.7 × 15 cm column, eluting with 100 mL CH_2Cl_2, 200 mL 1% MeOH/CH_2Cl_2, 200 mL 5% MeOH/CH_2Cl_2 then 10% MeOH/CH_2Cl_2. The product containing fractions were combined and then concentrated under reduced pressure to give clathridine A, **2.1a,** (0.080 mg, 66% yield) as a yellow oil. R_f = 0.55 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.69 (d, J = 7.3 Hz, 1H), 6.66 (s, 1H), 6.64 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H), 5.87 (s, 2H), 3.74 (s, 2H), 3.64 (s,

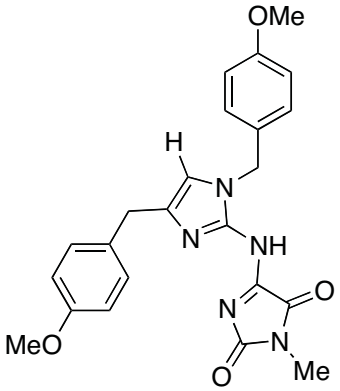
3H), 3.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.0, 155.0, 147.9, 147.1, 146.3, 144.2, 139.8, 132.8, 121.7, 117.7, 109.3, 108.4, 101.0, 34.5, 32.2, 24.8; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 32.2, 24.8; CH_2: 101.0, 34.5; CH_1: 121.7, 117.7, 109.3, 108.4; CH_0: 162.0, 155.0, 147.9, 147.1, 146.3, 144.2, 139.8, 132.8 ; IR (neat) 2922, 1792, 1736, 1667, 1620, 1565, 1501, 1488, 1443, 1391, 1308, 1246, 1213, 1115, 1037, 927, 809, 725, 701, 597 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{16}H_{16}N_5O_4$ (M+H) 342.1219, Obsd. 342.1202.



4 - ((4 - (4 - (benzyloxy)benzyl) - 1 - methyl - 1H - imidazol - 2 - yl)amino) - 1-methyl-1H-imidazole-2,5-dione 2.1b. Prepared to give **2.1b** (83% yield) as a red crystalline solid. mp = 189-190 ^{O}C; R_f = 0.61 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40–7.28 (m 5H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.43 (s, 1H), 5.00 (s, 2H), 3.79 (s, 2H), 3.69 (s, 3H), 3.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.3, 157.7, 155.6, 147.1, 139.5, 137.2, 131.2, 129.9, 129.6, 128.7, 128.1, 127.6, 117.6, 115.1, 70.2, 33.8, 32.2, 24.8; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 32.2, 24.8; CH_2: 70.2, 33.8; CH_1: 129.9, 128.7, 128.1, 127.6, 117.6, 115.1; CH_0: 162.3, 157.7, 155.6, 147.1, 139.5, 137.2, 131.2, 129.6; IR (neat) 3258, 3032, 2945, 1792, 1735, 1668, 1610, 1564, 1509, 1444, 1390, 1304, 1242, 1175, 1144, 1115, 1040, 1025, 910, 842, 776, 727, 698, 624, 529 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{22}H_{22}N_5O_3$ (M+H) 404.1736 Obsd. 404.1723.

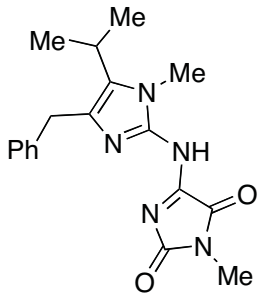


1-methyl-4-((1-methyl-4-(4-(trifluoromethyl)benzyl)-1H-imidazol-2-yl)amino)-1H-imidazole-2,5-dione 2.1c. Prepared to give **2.1c** (65% yield) as a yellow oil. R_f = 0.62 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 6.57 (s, 1H), 3.95 (s, 2H), 3.72 (s, 3H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.7, 154.1, 147.2, 143.5, 142.7, 139.3, 129.2, 125.7, 118.1, 113.3, 34.8, 32.2, 24.8; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 32.2, 24.8; CH_2: 34.8; CH_1: 129.2, 125.7, 118.1; CH_0: 161.7, 154.1, 147.2, 143.5, 142.7, 139.3, 113.3, 31.4; IR (neat) 2931, 2584, 2186, 1794, 1742, 1672, 1617, 1558, 1448, 1393, 1325, 1163, 1121, 1067, 1019, 726, 611 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{16}H_{14}F_3N_5O_2Na$ (M+Na) 388.1010, Obsd. 388.0997.



4-((4-benzyl-5-isopropyl-1-methyl-1H-imidazol-2-yl)amino)-1-methyl-1H-imidazole-2,5-dione 2.1d. Prepared to give **2.1d** (90% yield) as yellow solid. R_f = 0.20 (70% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.14 (app dd, *J* = 11.5, 8.0 Hz, 4H),

6.84 (dddd, J = 9.0, 3.0, 3.0, 3.0 Hz, 4H), 6.45 (s, 1H), 5.19 (s, 2H), 3.81 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.5 159.7, 158.4, 156.1, 146.9, 146.1, 139.6, 130.8, 129.9, 129.6, 128.4, 116.1, 114.4, 114.2, 55.5, 55.5, 48.6, 33.9, 25.0; IR (neat) 3249, 1789, 1737, 1666, 1611, 1512, 1449, 1392, 1335, 1246, 1116, 1041, 756, 650, 553 cm^{-1}



4-((4-benzyl-5-isopropyl-1-methyl-1H-imidazol-2-yl)amino)-1-methyl-1H-imidazole-2,5-dione 2.1e. Prepared to give **2.1e** (70% yield) as a yellow oil. R_f = 0.40 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12 (d, J = 1.3 Hz, 2H), 7.05–6.99 (m, 3H), 3.85 (s, 2H), 3.58 (s, 3H), 2.99 (s, 3H), 2.94 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.3, 153.0, 146.3, 133.3, 128.8, 128.4, 126.6, 33.2, 30.6, 25.1, 25.0, 24.9, 21.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 30.6, 25.0, 24.9, 21.5; CH_2: 33.2; CH_1: 128.8, 128.4, 126.6, 25.1; CH_0: 157.3, 153.0, 146.3, 133.3; IR (neat) 3340, 2924, 2854, 1784, 1727, 1678, 1460, 1395m 1345, 1149, 1040, 770, 721, 659, 613 cm^{-1}; HRMS *m/z* (ESI) Calculated $C_{18}H_{22}N_5O_2$ (M+H) 340.1774, Obsd. 340.1782.

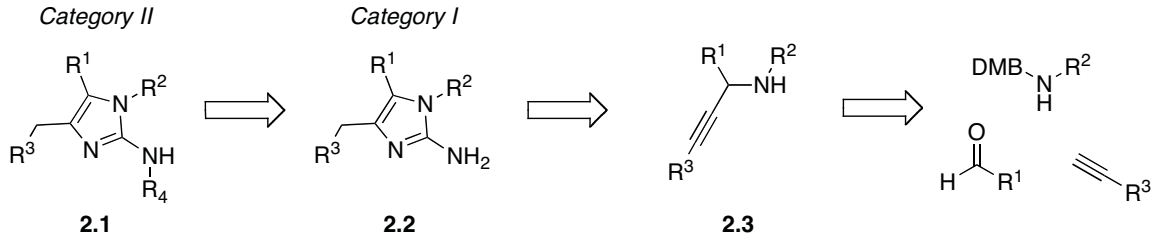


Figure 2.1. Revised retrosynthetic approach for 2-aminoimidazole access.

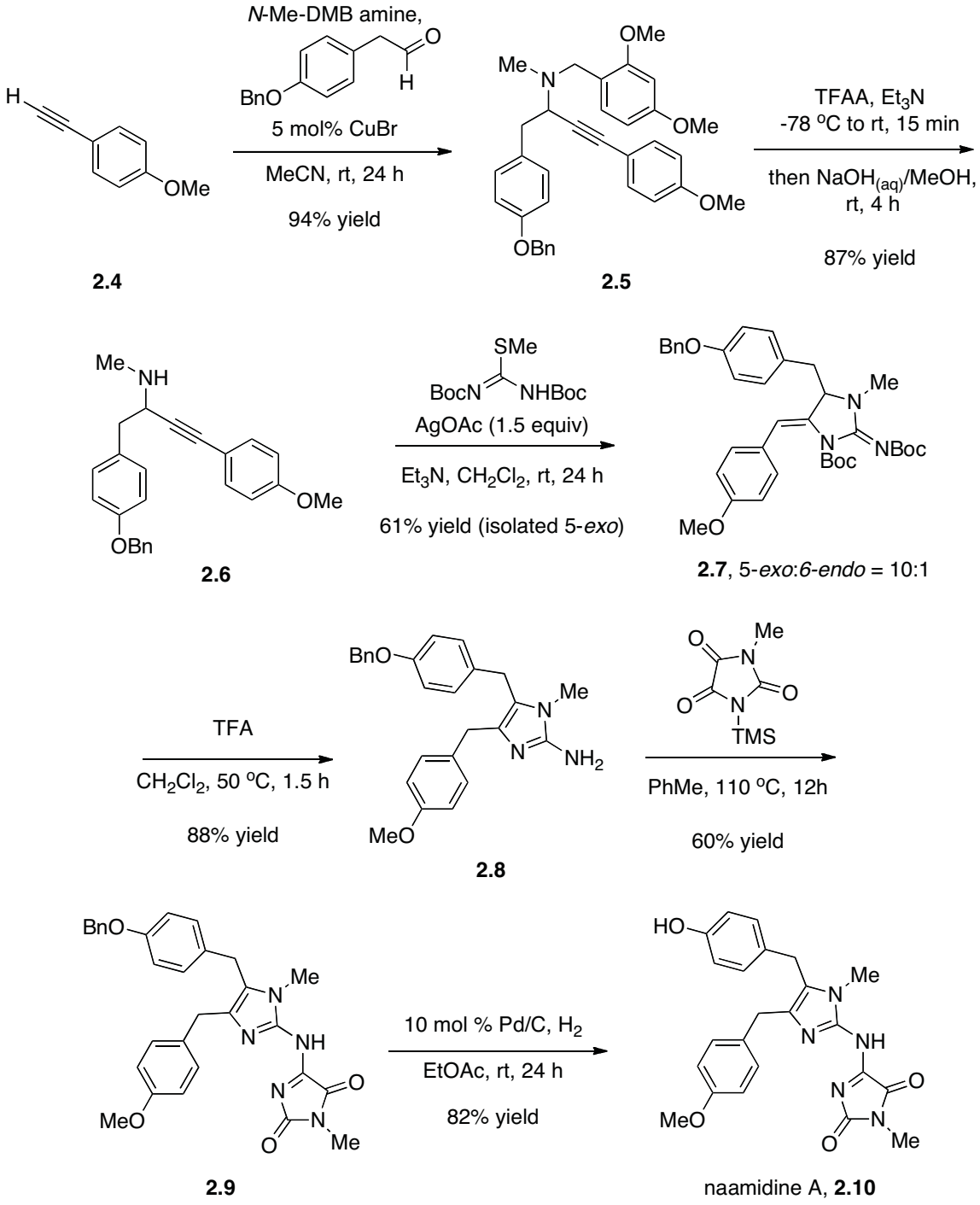
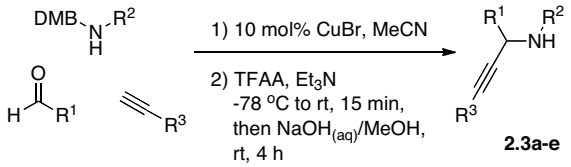


Figure 2.2. Synthesis of naamidine A.



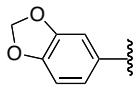
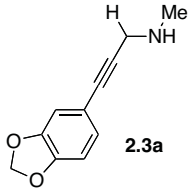
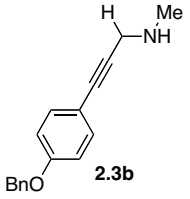
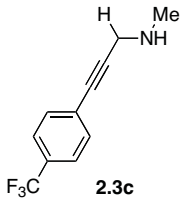
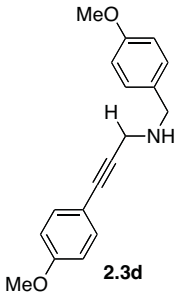
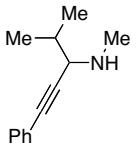
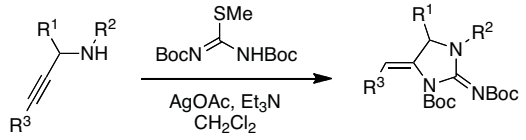
Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	Me		 **2.3a**	79
2	H	Me	*p*-BnOPh	 **2.3b**	70
3	H	Me	*p*-CF_3Ph	 **2.3c**	77
4	H	*p*-MeOBn	PMP	 **2.3d**	85
5	*i*Pr	Me	Ph	 **2.3e**	87

Figure 2.3. Synthesis of secondary propargylamines.



2.3a-e **2.11a-e**

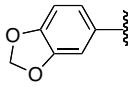
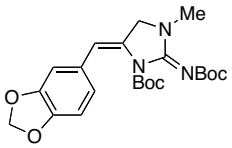
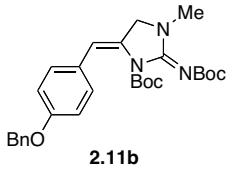
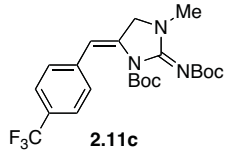
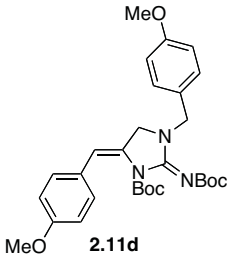
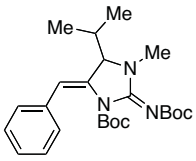
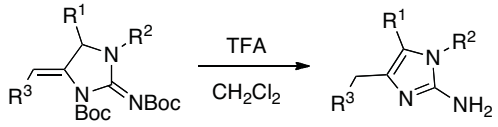
Entry	R^1	R^2	R^3	Product	5-*exo* : 6-*endo*	Yield (%)
1	H	Me		 **2.11a**	4:1	70
2	H	Me	*p*-BnOPh	 **2.11b**	>20:1	75
3	H	Me	*p*-CF_3Ph	 **2.11c**	>20:1	78
4	H	*p*-BnOBn	PMP	 **2.11d**	15:1	72
5	*i*Pr	Me	Ph	 **2.11e**	10:1	71

Figure 2.4. Synthesis of 5-*exo* cyclized Boc protected guanidines.



2.11a-e **2.2a-e**

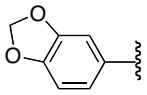
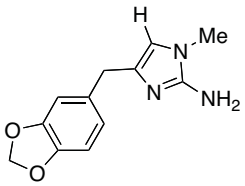
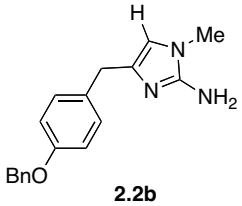
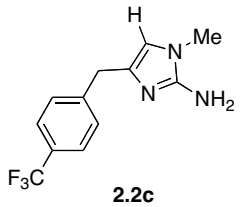
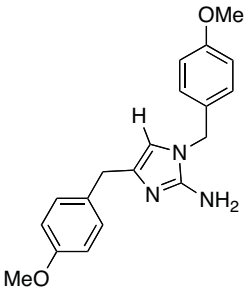
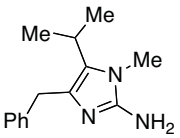
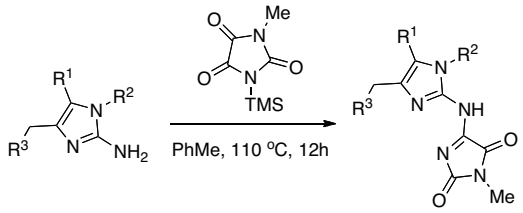
Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	Me		 preclathridine A, **2.2a**	91
2	H	Me	*p*-BnOPh	 **2.2b**	70
3	H	Me	*p*-CF_3Ph	 **2.2c**	97
4	H	*p*-MeOBn	PMP	 **2.2d**	35
5	*i*Pr	Me	Ph	 **2.2e**	88

Figure 2.5. Synthesis of *category I* primary amine access.



2.2a-e **2.1a-e**

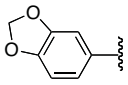
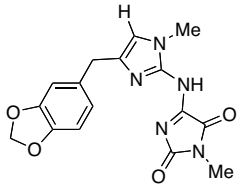
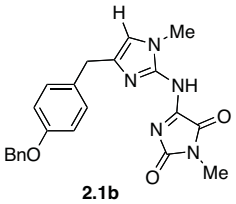
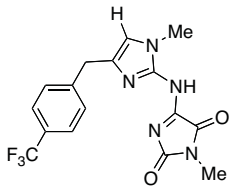
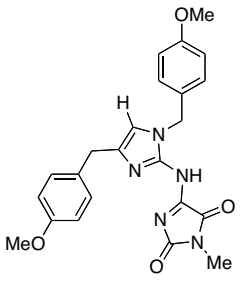
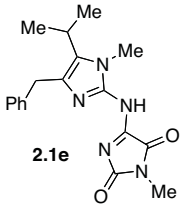
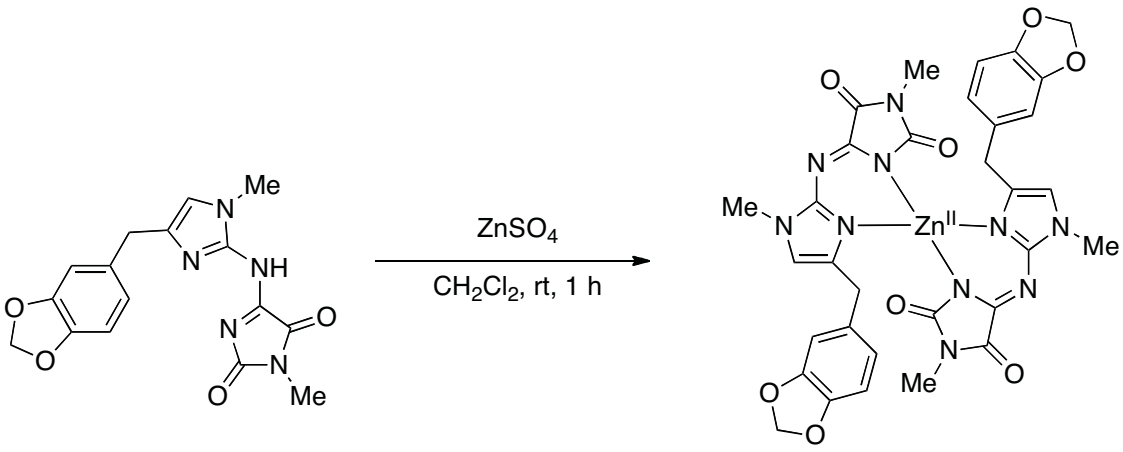
Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	Me		 clathridine A, **2.1a**	66
2	H	Me	*p*-BnOPh	 **2.1b**	83
3	H	Me	*p*-CF_3Ph	 **2.1c**	90
4	H	*p*-MeOBn	PMP	 isonaamidine C, **2.1d**	70
5	*i*Pr	Me	Ph	 **2.1e**	88

Figure 2.6. Addition of hydantoin tail to *category I* type intermediates.



2.1a, clathridine A

2.12, (clathridine A)$_2$Zn

Figure 2.8. Synthesis of Zinc dimer.

Entry	Compound	K_d (μM)
1	Naamidine A (**2.10)**	31.3
2	Clathridine A (**2.1a**)	8.3
3	Clathridine C	>500

Figure 2.9. Binding association of *category II* alkaloid natural products and zinc (II) triflate.

References

1. Gainer, M. J.; Newbold, N.; Looper, R. E. *Angew. Chem. Int. Ed.* **2011**, 50, 684–687.

2. Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 3116–3120.

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CHAPTER 3

EXPANSION OF 2-AMINOIMIDAZOLE CHEMISTRY: SYNTHESIS OF 2-THIO AND 2-OXOIMIDAZOLES

Introduction

2-thio and 2-oxoimidazoles represent a medicinally important heterocyclic scaffold. These target substructures are central to compounds possessing inhibitory activity against HIV-1 reverse transcriptase[1] and p38 MAP kinase[2] as well as histamine-H_3 antagonists (Figure 3.1).[3] They have also been documented as key pharmacophores in agents for the treatment of thrombosis,[4] inflammation and asthma.[5] The reaction sequence developed for access to 2-aminoimidazoles via a one-pot addition-hydroamination-isomerization sequence developed by Giles and coworkers[6] (Figure 3.2) was soon adapted to the addition of thiol, phenol and alcohol nucleophiles for the formation of 2-thio and 2-oxoimidazoles.[7]

Results and Discussion

One of the key aspects to this chemistry is the rapid preparation of the propargylcyanamide precursors (Figure 3.3). The propargylcyanamides (**3.2a-d**) used in this study were prepared in two steps by an iminium-acetylide three-component coupling

(3-CC) to give the propargylamines **3.1a-d**.[8] Cleavage of the tertiary amine with cyanogen bromide via von Braun reaction conditions gave the propargylcyanamides **3.2a-d** with cleavage of the intermediate cyanoammonium salt at the activated benzylic position of the PMB group.[9]

The addition of neutral thiols to initiate the addition-cyclization-isomerization sequence was initially investigated. After heating a solution of the propargylcyanamide **3.2a** with ethanethiol for 24 h, the formation of the desired product was observed, although approximately 5% of the propargylcyanamide had been converted. The poor electrophilic nature of *N,N*-dialkylcyanamides suggested that a Lewis acid catalyst or an anionic species would be required to affect addition to the cyanamide.[10,11] In contrast to the addition of amines to propargylcyanamides, lanthinum did not catalyze product formation.[6] Fortunately, the addition of 5 equiv of Hunig's base in the reaction mixture improved the nucleophilicity led to complete consumption of the propargylcyanamide after only 12 h at 120 ^{o}C to give 2-ethylthioimidazole **3.3a** in a 67% yield (Figure 3.4, entry 1). Treatment of the other cyanamides under the same conditions gave comparable results (entries 2-4). Benzylic thiols also gave the 2–thioimidazoles in moderate to good yields (Figure 3.4, entries 5-8).

Thiophenols are also competent partners in this reaction sequence (Figure 3.4, entries 9-12) and react chemoselectively in the presence of phenols (Figure 3.4, entries 13-16). For experimental convenience, an excess of thiol in the addition-cyclization-isomerization sequence was used; however, the use of dithiols in the presence of 1.5 equivalents of cyanamide per thiol was capable of producing bis-2-thioimidazoles **3.7a** and **3.7b** in good yields (Figure 3.5). Since it was noted that isopropanol was a

noncompetitive solvent for the lanthinum catalyzed addition of amines to cyanamides, it was not surprising to observe that they were not competent nucleophiles in the addition-cycloisomerization sequence under neutral conditions.[6]

The developed chemistry requires a fine balance of nucleophilicity and basicity to affect addition to the cyanamide without formation of the allenyl-cyanamide, which readily decomposes. The inclusion of an oxygen substituent bearing an adjacent sp^2 hybridized carbon atom allowed for broadened substituent diversity. It was previously observed that sterically hindered alkoxides (KO*t*Bu in THF) quantitatively isomerized propargylcyanamides to the allenyl-cyanamide in ~10 min at 0 ^{o}C. Due to the increased basicity of alkoxides relative to thiolates, which could favor isomerization over addition to the cyanamide, it was expected that phenoxides or alkoxides would not be competent nucleophiles in this chemistry. Contrary to this assumption, treatment of cyanamide **3.2a** with phenol in the presence of K_2CO_3 successfully delivered the 2-phenoxyimidazole (**3.8a**) in 77% yield (Figure 3.6). Toluene proved to be the best solvent for temperature considerations.

The nucleophile selection was then expanded to alkoxides quickly revealing that treatment of **3.2c** with MeOH and Hunig's base gave the methoxyimidazole **3.9a** in 72% yield (Figure 3.7, entry 1). Interestingly, *i*PrOH, the solvent choice for the La(III) catalyzed amine addition–hydroamination–isomerization manifold, afforded the 2–isopropoxyimidazole **3.9b** in 67% yield with the addition of KO*t*Bu (entry 2).

Conclusion

In conclusion, optimal conditions have been developed for the addition of both alkyl and aryl thiols and alcohols to propargylcyanamides. Subsequent cycloisomerization delivers the 2-thio- or 2-oxoimidazoles in good yields. The fact that equimolar KOtBu decomposes the substrates but catalytically generated nucleophiles (e.g., K_2CO_3/*i*PrOH) are competent partners suggests that thio- or oxo-nucleophiles with a pKa < ~18 should be tolerated under these conditions. Interestingly, La(III) does not influence the reaction of thio- or oxo-nucleophiles with propargylcyanamides, suggesting a unique catalytic role for La(III) in the addition-hydroamination-isomerization sequence with amines.

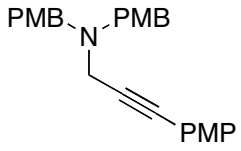
Experimental Section

General experimental procedures, materials and instrumentation

Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using flame-dried glassware. Triethylamine was distilled from CaH_2 immediately prior to use. Dichloromethane and toluene were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves.

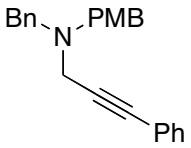
Yields were calculated for material judged homogeneous by thin-layer chromatography and ^{1}H NMR. Thin-layer chromatography was performed on Merck Kieselgel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV

lamp, and stained with either an ethanolic solution of 12-molybdophosphoric acid, *p*-anisaldehyde, or $KMnO_4$. Flash column chromatography was performed with Silicycle SiliaFlash® F60, slurry-packed with solvents indicated in glass columns. ^1H NMR spectra were recorded on Varian Unity-300, Inova-400, or VXR-500 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances are reported relative to $CDCl_3$, DMSO-d_5, HOD, or HD_2COD using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), coupling constant(s) (*J* in Hz), integral]. 1,2 ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak Infrared spectra were recorded on a Nicolet 380-FT IR spectrometer fitted with a SmartOrbit sample system. All absorptions are reported in cm^{-1} relative to polystyrene. Mass spectra were obtained at the University of Utah CIF on a Micromass Quattro II (ESI/APCI) for LRMS or an LCT XE premier (ESI/APCI-TOF) for HRMS.



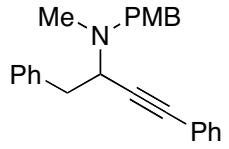
***N,N*-bis(4-methoxybenzyl)-3-(4-methoxyphenyl)prop-2-yn-1-amine 3.1a**. To a 100 mL round-bottomed flask containing a magnetic stir bar was added bis(4-methoxybenzyl)amine (PMB_2NH) (3.73 g, 14.5 mmol, 1.0 equiv.), 37% aqueous solution of formaldehyde (6.54 g, 6.00 mL, 80.6 mmol, 5.6 equiv.), 4-methoxyphenyl acetylene (2.02 g, 15.3 mmol, 1.06 equiv.), CuBr (0.209 g, 1.45 mmol, 0.1 equiv.) and MeCN (45 mL). The reaction mixture was allowed to stir at rt for 24 h. The reaction mixture was filtered through a plug of celite before the solvent was removed under reduced pressure.

Purification of the material was accomplished by flash column chromatography on a 5.7 × 15 cm column, eluting with 20% EtOAc/hexanes. The product containing fractions were combined and then concentrated under reduced pressure to give propargylamine **3.1a** (5.77 g, 98% yield) as a light yellow oil. R_f = 0.49 (35% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, *J* = 14 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 4H), 6.90-6.86 (m, 6H), 3.83 (s, 3H), 3.80 (s, 6H), 3.67 (s, 4H), 3.43 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 159.0, 133.4, 131.3, 130.5, 115.8, 114.2, 113.9, 85.8, 83.2, 57.1, 55.6, 55.5, 42.0; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: (2 × 55.4); CH_2: 57.0, 41.8; CH_1: 133.3, 132.3, 131.1, 114.0, 113.8; CH_0: 158.9, 85.8, 83.2; IR (neat): 2933, 2834, 1607, 1509, 1463, 1291, 1246, 1172, 1106, 1034, 832, 668 cm^{-1}. HRMS (ESI) Calculated for $C_{26}H_{28}NO_3$ *m/z* (M+H) 402.2069, Obsd. 402.2055.



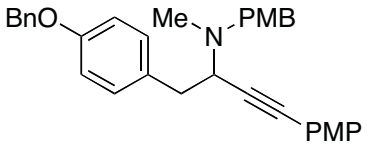
***N*-benzyl-*N*-(4-methoxybenzyl)-3-phenylprop-2-yn-1-amine 3.1b**. Obtained from the CuBr catalyzed 3-CC of formaldehyde, (PMB(Bn)NH), and phenylacetylene to give propargylamine **3.1b** as a clear as a clear oil in 90% yield. R_f = 0.25 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51-7.50 (m, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.35-7.31 (m, 6H), 7.23-7.25 (m, 4H), 6.88 (d, *J* = 8.3 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 2H), 3.69 (s, 2H), 3.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.9, 139.2,132.0, 131.1, 130.4, 129.3, (2 × 128.5), 128.2, 127.3, 123.7, 113.9, 86.1, 84.7, 57.8, 57.3, 55.5, 42.0; DEPT ^{13}C NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.5; CH_2: 57.8, 57.3, 42.0; CH_1: 132.0, 130.4, 129.3, (2 × 128.5), 128.2, 127.3, 113.9; CH_0: 159.9, 139.2, 131.1, 123.7, 86.1, 84.7; IR (neat): 3060, 3023, 2930, 2831, 1610, 1585, 1510, 1489, 1452, 1441,

1425, 1362, 1322, 1300, 1244, 1170, 1101, 1071, 1034, 972, 947, 912, 848, 808, 756, 739, 690, 638, 595, 580, 553 cm^{-1}. HRMS (ESI) Calculated for $C_{24}H_{24}NO$ *m/z* (M+H) 342.1858, Obsd. 342.1857.



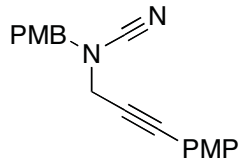
***N*-(4-methoxybenzyl)-*N*-methyl-1,4-diphenylbut-3-yn-2-amine 3.1c**. To a 100 mL high-pressure tube containing a magnetic stir bar was added phenylacetaldehyde (2.23 g, 18.3 mmol, 1.0 equiv), (4-methoxyphenyl)-*N*-methylmethanamine (PMB(Me)NH) (3.05 g, 18.3 mmol, 1.1 equiv), phenylacetylene (2.06 g, 2.22 mL, 20.2 mmol, 1.1 equiv), oven-dried molecular sieves, (Grade 564, 3 Å, 8-12 mesh) (*ca.* 10 g) and toluene (40 mL). The tube was then sealed and placed in a preheated 80 °C oil bath and was left to stir overnight. The reaction tube was then removed from the oil bath and left to cool to rt. To the reaction mixture was added CuBr (0.263 g, 1.83 mmol, 0.1 equiv) and the tube resealed and returned to the 80 °C oil bath. The reaction was allowed to proceed for 24 h at which time the high-pressure tube was removed from the oil bath and allowed to cool to rt. The crude reaction mixture was filtered through paper using a Buchner funnel and solids washed with EtOAc (100 mL). The filtrate collected and added to a separatory funnel containing water (100 mL) and hexanes (100 mL). The layers were separated and the organic layer washed with water (100 mL) and brine (100 mL). The organic layer was then collected, dried over Na_2SO_4, filtered and then concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 6.5 × 15 cm column, eluting with 150 mL of hexanes followed by 2 L of 10% EtOAc/hexanes (with 0.2% NH_4OH). The product containing fractions were combined

and then concentrated under reduced pressure to give propargylamine **3.1c** (6.19 g, 94% yield) as a light yellow oil. R_f = 0.24 (15% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.40 (m, 2H), 7.31-7.15 (m, 8H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.83 (dd, *J* = 8.3, 6.9 Hz, 1H), 3.77 (s, 3H), 3.70 (d, *J* = 13.0 Hz, 1H), 3.52 (d, *J* = 13.0 Hz, 1H), 3.05 (dd, *J* = 13.3, 6.9 Hz, 1H) 3.00 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.9, 139.0, 131.9, 131.3, 130.2, 129.6, 128.4, 128.3, 128.1, 126.5, 123.6, 113.8, 87.0, 86.9, 58.9, 57.8, 55.4, 40.6, 38.0; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 38.0; CH_2: 58.9, 40.6; CH_1: 131.9, 130.2, 129.6, 128.4, 128.3, 128.1, 126.5, 113.8, 57.8; CH_0: 158.9, 139.0, 131.3, 123.6, 87.0, 86.9; IR (neat): 3028, 2833, 1611, 1510, 1489, 1242, 1171, 1035, 756, 691 cm^{-1}. HRMS (ESI) Calculated for $C_{25}H_{26}NO$ *m/z* (M+H) 356.2014, Obsd. 356.2008.



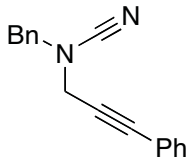
1-(4-(benzyloxy)phenyl)-*N*-(4-methoxybenzyl)-4-(4-methoxyphenyl)-*N*-methylbut- 3-yn-2-amine 3.1d. Obtained from the CuBr catalyzed 3-CC of 2-(4-(benzyloxy) phenyl)acetaldehyde, (4-methoxyphenyl)-*N*-methylmethanamine (PMB(Me)NH), and 1-ethynyl-4-methoxybenzene to give propargylamine **3.1d** as a yellow crystalline solid in 98% yield. R_f = 0.22 (40% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.27 (m, 7H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.84-6.78 (m, 4H), 5.03 (s, 2H), 3.78-3.74 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.50 (d, *J* = 13.0 Hz, 1H), 2.98 (dd, *J* = 12.8, 6.2 Hz, 1H), 2.93 (dd, *J* = 13.1, 8.1 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 158.8, 157.6, 137.4, 133.3, 131.5, 131.4, 130.6, 130.3, 128.7, 128.1, 127.6, 115.8, 114.7, 114.1, 113.8,

86.7, 85.5, 70.2, 58.9, 58.1, 55.5, 55.4, 39.8, 38.0; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.5, 55.4, 38.0; CH_2: 70.2, 58.9, 39.8; CH_1: 133.3, 130.6, 130.3, 128.7, 128.1, 127.7, 114.7, 114.1, 113.8, 58.1; CH_0: 159.5, 158.8, 157.6, 137.4, 131.5, 131.4, 115.8, 86.7, 85.5; IR (neat): 2950, 2835, 1607, 1509, 1454, 1289, 1244, 1173, 1033, 831, 734, 697 cm^{-1}. HRMS (ESI) Calculated for $C_{33}H_{34}NO_3$ *m/z* (M+H) 492.2539, Obsd. 492.2542.

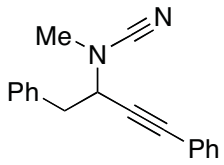


***N*-(4-methoxybenzyl)-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)cyanamide 3.2a**. To a 250 mL round-bottomed flask containing a magnetic stir bar was added propargylamine **3.1a** (5.030 g, 12.5 mmol, 1.0 equiv.), 3 M solution of CNBr in CH_2Cl_2 (8.40 mL, 25.1 mmol, 2.0 equiv.), K_2CO_3 (3.916 g, 28.33 mmol, 2.3 equiv.), and dioxane (125 mL). The reaction mixture was allowed to stir at rt for 24 h before being quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL). The reaction mixture was diluted in CH_2Cl_2 (100 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 5.7 × 15 cm column, eluting with 20% EtOAc/hexanes. The product containing fractions were combined and then concentrated under reduced pressure to give cyanamide **3.2a** (3.608 g, 94% yield) as a light yellow oil. R_f = 0.40 (35% EtOAc/hexanes). ^{1}H NMR (CDCl3, 500 MHz): δ 7.40 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 4.26 (s, 2H), 3.92 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.3,

160.2, 133.6, 130.7, 126.0, 117.7, 114.5, 114.4, 114.3, 114.2, 87.2, 80.1, 55.6, 55.5, 54.3, 41.1; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.6, 55.5; CH_2: 54.3, 41.1; CH_1: 133.6, 130.7, 114.5, 114.3; CH_0: 160.3, 160.2, 126.0, 117.7, 114.5, 114.4, 87.2, 80.1; IR (neat): 2931, 2836, 1721, 1643, 1612, 1585, 1512, 1491, 1453, 1407, 1359, 1302, 1247, 1223, 1175, 1145, 1107, 1078, 1034, 905 822, 758, 696 cm^{-1}. HRMS (ESI) Calculated for *m/z* $C_{19}H_{18}N_2NaO_2$ (M+Na) 329.1266, Obsd. 329.1263.

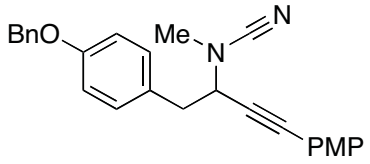


***N*-benzyl-*N*-(3-phenylprop-2-ynyl)cyanamide 3.2b**. Cyanamide **3.2b** was obtained as a light-yellow oil from the von Braun reaction of PMB propargylamine **3.1b** in 90% yield. R_f = 0.23 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.29 (m, 10H), 4.31 (s, 2H), 3.93 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.0, 132.1, (2 × 129.2), (2 × 129.1), 128.7, 122.1, 117.5, 87.4, 81.3, 54.8, 41.1; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_2: 54.8, 41.1; CH_1: 132.1, (2 × 129.2), (2 × 129.1), 128.7; CH_0: 134.0, 122.1, 117.5, 87.4, 81.3; IR (neat): 3032, 2212, 1720, 1598, 1489, 1455, 1442, 1339, 1258, 1107, 1027, 1002, 966, 765, 734 cm^{-1}. HRMS (ESI) Calculated for $C_{17}H_{14}N_2Na$ *m/z* (M+Na) 269.1055, Obsd. 269.1059.

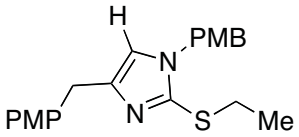


***N*-(1,4-diphenylbut-3-yn-2-yl)-*N*-methylcyanamide 3.2c**. Cyanamide **3.2c** was obtained from the von Braun reaction of PMB propargylamine **3.1c** as a light-yellow semi-crystalline solid in 87% yield. R_f = 0.56 (40% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$,

400 MHz): δ 7.43-7.39 (m, 2H), 7.36-7.25 (m, 8H), 4.10 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.20 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.15 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.1, 131.9, 129.5, 129.0, 128.8, 128.5, 127.4, 122.0, 116.8, 87.6, 84.2, 56.6, 40.3, 37.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 37.7; CH_2: 40.3; CH_1: 131.9, 129.5, 129.0, 128.8, 128.5, 127.4, 56.6; CH_0: 136.1, 122.0, 116.8, 87.6, 84.2; IR (neat): 3030, 2930, 2210, 1598, 1489, 1454, 1442, 1372, 1032, 723, 691 cm^{-1}. HRMS (ESI) Calculated for *m/z* $C_{18}H_{16}N_2Na$ (M+Na) 283.1211, Obsd. 283.1212.

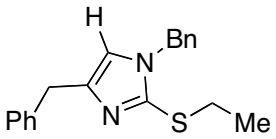


***N*-(1-(4-(benzyloxy)phenyl)-4-(4-methoxyphenyl)but-3-yn-2-yl)-*N*-methylcyanamide 3.2d**. Cyanamide **3.2d** was obtained as a yellow crystalline solid from the von Braun reaction of PMB propargylamine **3.1d** in 76% yield. R_f = 0.41 (40% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.32 (m, 5H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.05, (s, 2H), 4.04 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.81 (s, 3H), 3.13 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.09 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 158.2, 137.2, 133.5, 130.7, 128.8, 128.6, 128.1, 127.7, 117.0, 115.1, 114.2, 114.1, 87.6, 83.0, 70.2, 56.9, 55.5, 39.7, 37.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.5, 37.7; CH_2: 70.2, 39.7; CH_1: 133.5, 130.7, 128.8, 128.2, 127.7, 115.1, 114.2, 56.9; CH_0: 160.2, 158.2, 137.2, 128.6, 117.0, 114.1, 87.6, 83.0; IR (neat): 3034, 2933, 2837, 2211, 1605, 1584, 1291, 1247, 1174, 833, 740, 697 cm^{-1}. HRMS (ESI) Calculated for $C_{26}H_{24}N_2NaO_2$ *m/z* (M+Na) 419.1735, Obsd. 419.1743.

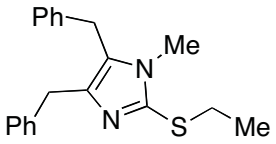


2-(ethylthio)-1,4-bis(4-methoxybenzyl)-1*H*-imidazole 3.3a. To a 15 mL high-pressure tube containing a magnetic stir bar was added cyanamide **3.2a** (0.1065 g, 0.347 mmol, 1.0 equiv.), ethanethiol (0.2158 g, 260 mL, 3.47 mmol, 10.0 equiv.), *i*Pr_2EtN (0.6735 g, 910 mL, 5.21 mmol, 15.0 equiv.) and isopropanol (2 mL). The high-pressure tube was then sealed and placed in a preheated 120 °C oil bath. After 24 h at 120 °C, the high-pressure was removed from the oil bath and left to cool to rt. The crude reaction mixture was diluted in CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 2.5 × 15 cm column, eluting with 35% EtOAc/hexanes (with 3% Et_3N). The product containing fractions were combined and then concentrated under reduced pressure to give 2-thioimidazole **3.3a** (0.0861 g, 67% yield) as a light yellow oil. R_f = 0.24 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H) 6.42 (s, 1H), 4.96 (s, 2H), 3.80 (s, 2H), 3.73 (s, 6H), 2.94 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 158.0, 143.5, 140.5, 132.2, 130.0, 128.9, 128.7, 118.3, 114.3, 113.8, (2 × 55.4), 49.7, 34.4, 29.5, 15.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: (2 × 55.4), 15.7; CH_2: 49.7, 34.4, 29.5; CH_1: 130.0, 128.7, 118.3, 114.3, 113.8; CH_0: 159.3, 158.0, 143.5, 140.5, 132.2, 128.9; IR (neat): 2931, 2834, 1612, 1584, 1512, 1453, 1300, 1247, 1176, 1106, 1034, 794 cm^{-1}. HRMS (ESI) Calculated for $C_{21}H_{25}N_2O_2S$ *m/z* (M+H) 369.1637, Obsd.

369.1641.

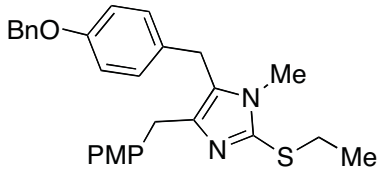


1,4-dibenzyl-2-(ethylthio)-1*H*-imidazole 3.3b. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2b** and ethanethiol to give 2-thioimidazole **3.3b** as a light-yellow oil in 77% yield. R_f = 0.38 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.18 (m, 8H), 7.11-7.10 (m, 2H), 6.50 (s, 1H), 5.09 (s, 2H), 3.92 (s, 2H), 2.98 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.3, 141.0, 140.2, 137.0, 129.2, 129.0, 128.6, 128.1, 127.3, 126.3, 118.7, 50.3, 35.5, 29.6, 15.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 15.2; CH_2: 50.3, 35.5, 29.6; CH_1: 129.2, 129.0, 128.6, 128.1, 127.3, 126.3, 118.7; CH_0: 143.3, 141.0, 140.2, 137.0; IR (neat): 3028, 2928, 2362, 1676, 1603, 1559, 1495, 1453, 1419, 1356, 1300, 1262, 1201, 1175, 1107, 1075, 1029, 732, 697, 668 cm^{-1}. HRMS (ESI) Calculated for *m/z* $C_{19}H_{21}N_2S$ (M+H) 309.1425, Obsd. 309.1431.

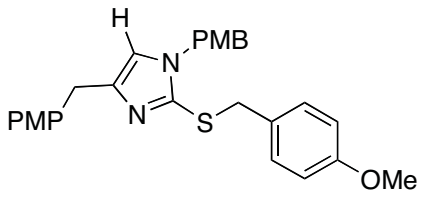


4,5-dibenzyl-2-(ethylthio)-1-methyl-1*H*-imidazole 3.3c. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2c** and ethanethiol to give 2-thioimidazole **3.3c** as a light-yellow oil in 93% yield. R_f = 0.46 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.14 (m, 8H), 6.96-6.95 (m, 4H), 3.96 (s, 2H), 3.89 (s, 2H), 3.33 (s, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.9, 139.5, 139.0, 138.1, 128.8, 128.7, 128.4, 128.1, 126.6, 125.9, 83.0, 33.9, 31.4, 30.0, 29.5, 15.1; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ

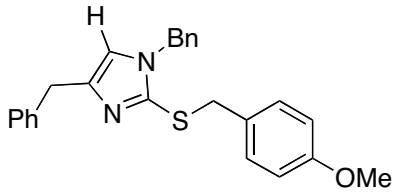
CH_3: 31.4, 15.1; CH2: 33.9, 30.0, 29.5; CH_1: 128.8, 128.7, 128.4, 128.1, 126.6, 125.9; CH_0: 140.9, 139.5, 139.0, 138.1, 83.0; IR (neat): 3060, 3026, 2965, 2926, 1602, 1494, 1454, 1376, 1264, 1112, 1074, 1029, 739, 696 cm^{-1}. HRMS (ESI) Calculated for $C_{20}H_{23}N_2S$ *m/z* (M+H) 323.1582, Obsd. 323.1583.



5-(4-(benzyloxy)benzyl)-2-(ethylthio) - 4 - (4-methoxybenzyl)-1-methyl-1*H*-imidazole 3.3d. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2d** and ethanethiol to give 2-thioimidazole **3.3d** as a light-yellow oil in 82% yield. R_f = 0.35 (40% EtOAc/hexanes, with 1% Et_3N). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.28 (m, 5H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 4.99 (s, 2H), 3.88 (s, 2H), 3.81 (s, 2H), 3.73 (s, 3H), 3.31 (s, 3H), 2.95 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.9, 157.6, 139.4, 139.3, 137.1, 133.2, 130.5, 129.6, 129.1, 128.7, 128.1, 128.1, 127.6, 115.1, 113.8, 70.2, 55.4, 33.1, 31.4, 29.5, 29.2, 15.1; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 31.3, 15.1; CH_2: 70.2, 33.1, 29.5, 29.2; CH_1: 129.6, 129.1, 128.7, 128.1, 127.6, 115.1, 113.8; IR (neat): 2928, 2833, 1722, 1608, 1583, 1508, 1452, 1378, 1240, 1173, 1026, 804, 734, 696 cm^{-1}. HRMS (ESI) Calculated for $C_{28}H_{31}N_2O_2S$ *m/z* (M+H) 459.2106, Obsd. 459.2095.

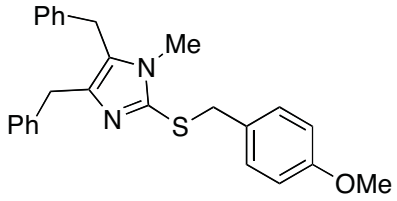


1,4-bis(4-methoxybenzyl)-2-(4-methoxybenzylthio)-1*H*-imidazole 3.4a. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2a** and (4-methoxyphenyl)methanethiol to give 2-thioimidazole **3.4a** as a light-yellow oil in 82% yield. R_f = 0.19 (35% EtOAc/hexanes with 1% Et_3N); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.41 (s, 1H), 4.69, (s, 2H), 4.10 (s, 2H), 3.85 (s, 2H), 3.76 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 159.0, 158.1, 143.7, 139.7, 132.4, 130.2, 129.9, 128.8, 128.8, 118.2, 114.2, 114.0, 113.8, 55.4, 55.4, 49.5, 39.9, 34.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.4; CH2: 49.5, 39.9, 34.5; CH_1: 130.2, 129.3, 128.8, 118.2, 114.2, 114.0, 113.8; IR (neat): 2933, 2834, 1610, 1511, 1463, 1301, 1245, 1175, 1107, 1033, 834, 795 cm^{-1}. HRMS (ESI) Calculated for $C_{27}H_{29}N_2O_3S$ *m/z* (M+H) 461.1899, Obsd. 461.1899.

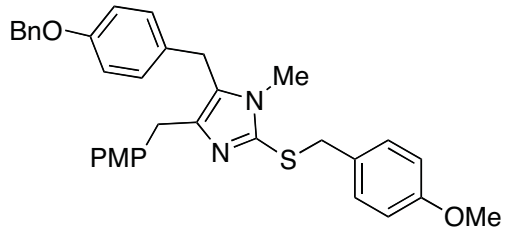


1,4-dibenzyl-2-(4-methoxybenzylthio)-1*H*-imidazole 3.4b. Obtained from the *N,N*-diisopropylethylamine catalyzed addition reaction of cyanamide **3.2b** and 4-(methoxyphenyl)methanethiol to give 2-thioimidazole **3.4b** as a light yellow oil in 71% yield. R_f = 0.26 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31-7.18 (m, 8H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 6.9 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.46 (s, 1H), 4.78 (s, 2H) 4.10 (s, 2H), 3.93 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 143.4, 140.4, 140.1, 136.8, 130.3, 130.0, 129.1, 129.0,

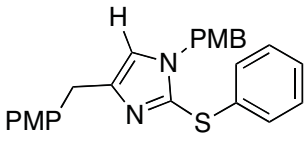
128.5, 128.0, 127.4, 126.3, 118.6, 114.1, 55.5, 50.1, 40.0, 35.4; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.5; CH_2: 50.1, 40.0, 35.4; CH_1: 130.3, 129.1, 129.0, 128.5, 128.0, 127.4, 126.3, 118.6, 114.1; CH_0: 159.1, 143.4, 140.4, 140.1, 136.8 130.0; IR (neat): 3061, 3028, 2932, 2834, 1609, 1583, 1495, 1453, 1422, 1354, 1301, 1249, 1175, 1105, 1074, 1031, 833, 731, 697, 660, 548 cm^{-1}. HRMS (ESI) Calculated for $C_{25}H_{25}N_2OS$ *m/z* (M+H) 401.1688, Obsd. 401.1693.



4,5-dibenzyl-2-(4-methoxybenzylthio)-1-methyl-1*H*-imidazole 3.4c. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2c** and 4-(methoxyphenyl)methanethiol to give 2-thioimidazole **3.4c** as a light-yellow oil in 97% yield. R_f = 0.26 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.14 (m, 8H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.85 (m, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.00 (s, 2H), 3.97 (s, 2H), 3.80 (s, 2H), 3.69 (s, 3H), 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.9, 140.9, 139.6, 138.3, 138.0, 130.3, 130.1, (2 ´ 128.7), 128.4, 128.2, 128.1, 126.5, 126.0, 113.8, 55.3, 40.3, 34.0, 31.1, 30.0; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.3, 31.1; CH_2: 40.3, 34.0, 30.0; CH_1: 130.1, 128.7, 128.4, 128.1, 126.5, 126.0, 113.8; CH_0: 158.9, 140.9, 139.6, 138.3, 138.0, 130.3, 128.7, 128.2; IR (neat): 3028, 2932, 2835, 1706, 1608, 1583, 1511, 1494, 1453, 1383, 1301, 1247, 1174, 1106, 1075, 1030, 912, 833, 728, 695, 658 cm^{-1}; HRMS (ESI) Calculated for $C_{26}H_{27}N_2OS$ *m/z* (M+H) 415.1844, Obsd. 415.1852.

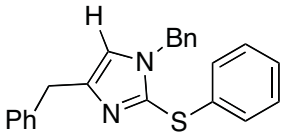


5-(4-(benzyloxy)benzyl)-4-(4-methoxybenzyl)-2-(4-methoxybenzylthio)-1-methyl-1*H*-imidazole 3.4d. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2d** and 4-(methoxyphenyl)methanethiol to give 2-thioimidazole **3.4d** as a light-yellow oil in 53% yield. R_f = 0.10 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.36 (m, 4H), 7.33-7.30 (m, 1H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.80-6.75 (m, 4H) 6.63 (d, *J* = 8.3 Hz, 2H), 5.01 (s, 2H), 4.00 (s, 2H), 3.90 (s, 2H), 3.76 (s, 3H), 3.75 (s, 2H), 3.70 (s, 3H), 2.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.9, 158.0, 157.6, 139.9, 138.1, 137.1, 133.2, 130.4, 130.3, 130.1, 129.6, 129.1, 128.8, 128.5, 128.2, 127.7, 115.0, 114.1, 113.9, 113.8, 70.2, 55.4, 55.3, 40.3, 33.1, 31.1, 29.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.3, 31.1; CH_2: 70.2, 40.3, 33.1, 29.2; CH_1: 130.1, 129.6, 129.1, 128.8, 128.2, 127.7, 115.0, 113.9, 113.8; CH_0: 158.9, 158.0, 157.6, 139.9, 138.1, 137.1, 133.2, 130.4, 130.3, 128.5, 114.1; IR (neat): 2932, 2835, 1703, 1608, 1583, 1509, 1453, 1381, 1301, 1239, 1174, 1107, 1027, 918, 830, 733, 697, 653, 608 cm^{-1}. HRMS (ESI) Calculated for $C_{34}H_{35}N_2O_3S$ *m/z* (M+H) 551.2368, Obsd. 551.2363.

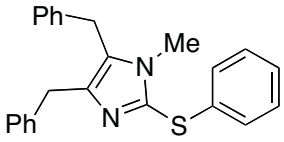


1,4-bis(4-methoxybenzyl)-2-(phenylthio)-1*H*-imidazole 3.5a. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2a** and thiophenol

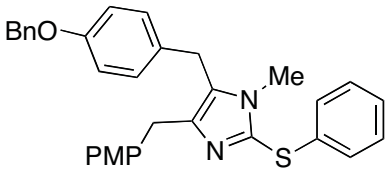
to give 2-thioimidazole **3.5a** as a light-yellow oil in 83% yield. R_f = 0.38 (35% EtOAc/hexanes with 1% Et3N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.17 (m, 4H), 7.16-7.10 (m, 3H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.60 (s, 1H), 5.00 (s, 2H), 3.89 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4, 158.1, 144.4, 136.7, 135.7, 132.1, 130.0, 129.3, 129.1, 128.4, 127.9, 126.5, 119.7, 114.2, 113.9, 55.4, 55.4, 50.3, 34.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.4; CH_2: 50.3, 34.5; CH_1: 130.0, 129.3, 129.1, 127.9, 126.5, 119.7, 114.2, 113.9; CH_0: 159.4, 158.1, 144.4, 136.7, 135.7, 132.1, 128.4; IR (neat): 2932, 2835, 1721, 1610, 1510, 1478, 1440, 1301, 1243, 1174, 1030, 736, 689 cm^{-1}. HRMS (ESI) Calculated for $C_{25}H_{25}N_2O_2S$ *m/z* (M+H) 417.1637, Obsd. 417.1632.



1,4-dibenzyl-2-(phenylthio)-1*H*-imidazole 3.5b. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2b** and thiophenol to give 2-thioimidazole **3.5b** as a light-yellow oil in 91% yield. R_f = 0.50 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, *J* = 4.5 Hz, 4H), 7.26-7.21 (m, 6H), 7.17-7.14 (m, 3H), 7.00-6.97 (m, 2H), 5.10 (s, 2H), 3.97 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.1, 140.1, 136.4, 135.5, 131.7, 129.4, 129.1, 129.0, 128.6, 128.2, 128.1, 127.6, 126.7, 126.4, 120.2, 50.9, 35.5; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_2: 50.9, 35.5; CH_1: 129.4, 129.1, 129.0, 128.6, 128.2, 128.1, 127.6, 126.7, 126.4, 120.2; CH_0: 144.1, 140.1, 136.4, 135.5, 131.7; IR (neat): 3060, 3029, 1721, 1580, 1494, 1477, 1453, 1440, 1417, 1344, 1302, 1234, 1155, 1121, 1080, 1024, 731 cm^{-1}. HRMS (ESI) Calculated for $C_{23}H_{21}N_2S$ *m/z* (M+H) 357.1425, Obsd. 357.1432.

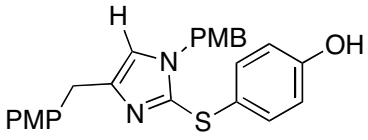


4,5-dibenzyl-1-methyl-2-(phenylthio)-1*H*-imidazole 3.5c. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2c** and thiophenol to give 2-thioimidazole **3.5c** as a light-yellow oil in 94% yield. R_f = 0.36 (35% EtOAc/hexanes with 1% Et_3N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.27 (m, 2H), 7.26-7.09 (m, 9H), 7.07-7.04 (m, 2H), 6.95-6.91 (m, 2H), 4.02 (s, 2H), 3.92 (s, 2H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.7, 140.3, 139.9, 137.7, 135.8, 129.8, 129.3, 128.8, 128.7, 128.5, 128.0, 127.2, 126.7, 126.2, 126.1, 34.1, 31.7, 30.2; ^{13}C NMR DEPT ($CDCl_3$, 125 MHz): δ CH_3: 31.7; CH_2: 34.1, 30.2; CH_1: 129.3, 128.8, 128.7, 128.5, 128.0, 127.2, 126.7, 126.2, 126.1; CH_0: 140.7, 140.3, 139.9, 137.7, 135.8; IR (neat): 3059, 3025, 2914, 1602, 1581, 1493, 1478, 1453, 1439, 1404, 1374, 1074, 1024, 736, 689 cm^{-1}. HRMS (ESI) Calculated for $C_{24}H_{23}N_2S$ *m/z* (M+H) 371.1582, Obsd. 371.1581.

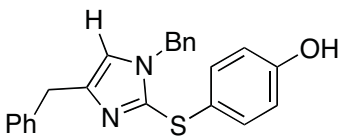


5-(4-(benzyloxy)benzyl)-4-(4-methoxybenzyl)-1-methyl-2-(phenylthio)-1*H*-imidazole 3.5d. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2d** and thiophenol to give 2-thioimidazole **3.5d** as a light-yellow oil in 87% yield. R_f = 0.32 (35% EtOAc/hexanes with 1% Et_3N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.34 (m, 4H), 7.33-7.28 (m, 1H), 7.23-7.17 (m, 4H), 7.13-7.09 (m, 1H), 7.06-7.03 (m, 2H), 6.86-6.81 (m, 4H), 6.80-6.77 (m, 2H), 5.00 (s, 2H), 3.94 (s, 2H), 3.85 (s, 2H), 3.74 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.0, 157.6, 140.5, 137.1,

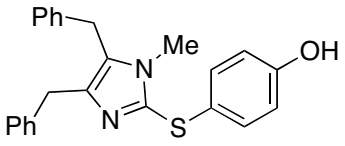
136.1, 135.6, 132.9, 130.3, 130.0, 129.6, 129.3, 129.0, 128.7, 128.1, 127.6, 127.2, 126.2, 115.2, 113.9, 70.2, 55.4, 33.2, 31.7, 29.4; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 31.7; CH_2: 70.2, 33.2, 29.4; CH_1: 129.6, 129.3, 129.0, 128.7, 128.1, 127.6, 127.2, 126.2, 115.2, 113.9; CH_0: 158.0, 157.6, 140.5, 137.1, 136.1, 135.6, 132.9, 130.3, 130.0; IR (neat): 3031, 2907, 2833, 1609, 1582, 1508, 1478, 1378, 1240, 1173, 1024, 804, 735, 691 cm^{-1}. HRMS (ESI) Calculated for $C_{32}H_{31}N_2O_2S$ *m/z* (M+H) 507.2106, Obsd. 507.2110.



4-(1,4-bis(4-methoxybenzyl)-1*H*-imidazol-2-ylthio)phenol 3.6a. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2a** and 4-mercaptophenol to give 2-thioimidazole **3.6a** as a light-yellow oil in 74% yield. R_f = 0.06 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12-7.11 (m, 4H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.53 (s, 1H), 6.29 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C NMR ($CDCl^3$, 125 MHz): δ 158.6, 158.2, 143.3, 134.2, 131.4, 130.0, 129.0, 128.3, 118.3, 117.0, 114.4, 113.9, 55.4, 55.3, 50.2, 33.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.3; CH_2: 50.2, 33.7; CH_1: 134.2, 130.0, 129.0, 117.0, 114.4, 113.9; CH_0: 158.6, 158.2, 143.3, 131.4, 128.3, 118.3; IR (neat): 2931, 2836, 2001, 1612, 1583, 1513, 1495, 1442, 1356, 1247, 1177, 1933, 828 cm^{-1}. HRMS (ESI) Calculated for $C_{25}H_{25}N_2O_3S$ *m/z* (M+H) 433.1586, Obsd. 433.1586.

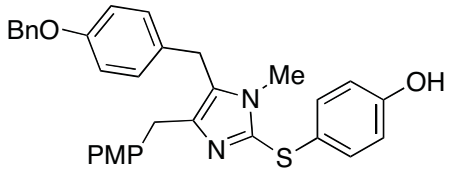


4-(1,4-dibenzyl-1*H*-imidazol-2-ylthio)phenol 3.6b. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2b** and 4-mercaptophenol to give 2-thioimidazole **3.6b** as a light-yellow oil in 64% yield. R_f = 0.12 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.31 (m, 3H), 7.26-7.16 (m, 8H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 6.34 (d, *J* = 8.8 Hz, 2H), 5.26 (s, 2H), 3.91 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 142.9, 142.3, 139.4, 136.4, 134.4, (2 × 129.2), 128.7, 128.4, 127.6, 126.5, 119.7, 118.8, 117.2, 50.8, 34.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_2: 50.8, 34.7; CH_1: 134.4, (2 × 129.2), 128.7, 128.4, 127.6, 126.5, 118.8, 117.2; CH_0: 159.0, 142.9, 142.3, 139.4, 136.4, 119.7; IR (neat): 3061, 3029, 2780, 2655, 1599, 1580, 1453, 1418, 1359, 1273, 1236, 1168, 830, 732, 697 cm^{-1}. HRMS (ESI) Calculated for $C_{23}H_{21}N_2OS$ *m/z* (M+H) 373.1357, Obsd. 373.1374.

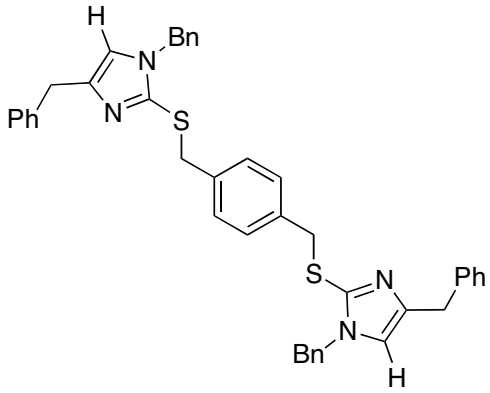


4-(4,5-dibenzyl-1-methyl-1*H*-imidazol-2-ylthio)phenol 3.6c. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2c** and 4-mercaptophenol to give 2-thioimidazole **3.6c** as a light-yellow oil in 77% yield. R*f* = 0.15 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.18 (m, 8H), 6.97 (dd, *J* = 7.3, 4.0 Hz, 2H), 6.94-6.92 (m, 2H), 6.33 (d, *J* = 8.3 Hz, 2H), 3.96 (s, 2H), 3.95 (s, 2H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.1, 140.2, 139.2, 137.7, 133.2, 129.0, 128.8, 128.6, 128.1, 126.9, 126.3, 117.0, 33.5, 32.0, 30.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 32.0; CH_2: 33.5, 30.2; CH_1: 133.2, 129.0, 128.8, 128.6, 128.1, 126.9, 126.3, 117.0; CH_0: 158.1, 140.2, 139.2, 137.7; IR (neat): 3059, 3026, 2920, 1722, 1639, 1602, 1494, 1454, 1383, 1236, 1111, 1029, 743, 726, 697 cm^{-1}. HRMS (ESI) Calculated

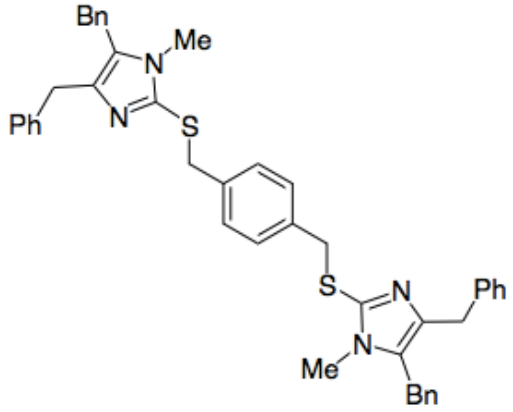
for $C_{24}H_{23}N_2OS$ *m/z* (M+H) 387.1531, Obsd. 387.1531.



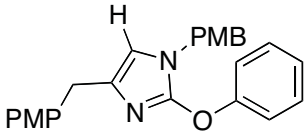
4 - (5 - (4 - (benzyloxy)benzyl) - 4 - (4 - methoxybenzyl) - 1-methyl - 1*H* - imidazol-2-ylthio)phenol 3.6d. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2d** and 4-mercaptophenol to give 2-thioimidazole **3.6d** as a light-yellow oil in 78% yield. R_f = 0.06 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.33 (m, 5H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.88 (s, 4H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 2H), 3.90 (s, 2H), 3.87 (s, 2H), 3.71 (s, 3H), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.3, 158.1, 157.8, 140.4, 139.3, 137.1, 133.3, 132.4, 130.0, 129.7, 129.2, 128.8, 128.7, 128.2, 127.7, 120.8, 117.0, 115.3, 114.0, 70.3, 55.5, 32.6, 32.0, 29.3; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.5, 32.0; CH_2: 70.3, 32.6, 29.3; CH_1: 133.3, 129.7, 129.2, 128.8, 128.7, 127.7, 117.0, 115.3, 114.0; CH_0: 158.3, 158.1, 157.8, 140.4, 139.3, 137.1, 132.4, 130.0, 128.2, 120.8; IR (neat): 2926, 2160, 1610, 1582, 1510, 1495, 1452, 1381, 1274, 1245, 1175, 1118, 1034, 828, 737, 697 cm^{-1}. HRMS (ESI) Calculated for $C_{32}H_{30}N_2O_3S$ *m/z* (M+H) 522.1977, Obsd. 522.2056.



1,4-bis((1,4-dibenzyl-1*H*-imidazol-2-ylthio)methyl)benzene 3.7a. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2b** and 1,4-phenylenedimethanethiol to give 2-thioimidazole **3.7b** as a light-yellow oil in 71% yield. R_f = 0.16 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.18 (m, 16H), 7.00 (s, 4H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 6.5 Hz, 2H), 6.47 (s, 2H), 4.75 (s, 4H), 4.11 (s, 4H), 3.93 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.3, 140.1, 139.8, 136.9, 136.5, 129.2, (2 × 129.0), 128.5, 128.0, 127.2, 126.2, 118.7, 50.0, 40.0, 35.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_2: 50.0, 40.0, 35.2; CH_1: 136.5, 129.2, (2 × 129.0), 128.5, 128.0, 127.2, 126.2, 118.7; CH_0: 143.3, 140.1, 139.8, 136.9, 136.5; IR (neat): 3061, 3027, 2926, 1603, 1558, 1511, 1495, 1453, 1420, 1355, 1299, 1241, 1201, 1104, 1074, 1029, 821, 697 cm^{-1}. HRMS (ESI) Calculated for $C_{42}H_{39}N_4S_2$ *m/z* (M+H) 663.2616, Obsd. 663.2623.

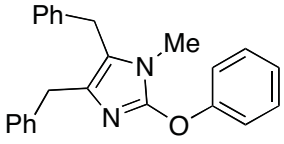


1,4-bis((4,5-dibenzyl-1-methyl-1*H*-imidazol-2-ylthio)methyl)benzene 3.7b. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2c** and 1,4-benzene dimethanethiol to give 2-thioimidazole **3.7a** as a colorless crystalline solid in 73% yield. R_f = 0.11 (35% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20-7.08 (m, 16H), 6.80 (d, *J* = 6.0 Hz, 4H), 6.69 (s, 4H); 3.92 (s, 4H), 3.88 (s, 4H), 3.74 (s, 4H), 2.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.0, 139.7, 138.1, 137.3, 129.0, (2 × 128.8), 128.5, 128.2, 126.8, 126.1, 40.5, 34.1, 31.1, 30.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 31.1; CH_2: 40.5, 34.1, 30.2; CH_1: 129.0, (2 × 128.8), 128.5, 128.2, 126.8, 126.1; CH_0: 141.0, 139.7, 138.1, 137.3; IR (neat): 3026, 2917, 2848, 2182, 1969, 1599, 1582, 1494, 1460, 1452, 1433, 1275, 1244, 826, 743, 726, 696 cm^{-1}. HRMS (ESI) Calculated for $C_{44}H_{43}N_4S_2$ *m/z* (M+H) 691.2929, Obsd. 691.2936.



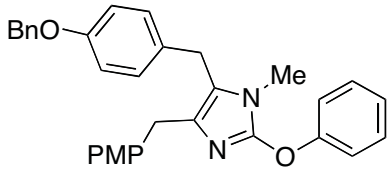
1,4-bis(4-methoxybenzyl)-2-phenoxy-1*H*-imidazole 3.8a. In a 15 mL high-pressure tube containing a magnetic stir bar was added cyanamide **3.2a** (0.1201 g, 0.392 mmol, 1.0 equiv.), phenol (0.1107 g, 0.1.18 mmol, 3.0 equiv.), K_2CO_3 (0.2709 g, 1.96 mmol, 5.0

equiv.) and toluene (1.5 mL). The high-pressure tube was then sealed and placed in a preheated 150 °C oil bath. After 24 h at 150 °C, the high-pressure was removed from the oil bath and left to cool to rt. The crude reaction mixture was diluted in CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 2.5 × 15 cm column, eluting with 350 mL of 25% EtOAc/hexanes (with 1% Et_3N). The product containing fractions were combined and then concentrated under reduced pressure to give 2-oxoimidazole **3.8a** (0.1206 g, 77% yield) as a light yellow oil. R_f = 0.43 (40% EtOAc/hexane with 1% Et_3N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dd, *J* = 7.3, 8.8 Hz, 2H), 7.20-7.14 (m, 4H), 7.13-7.07 (m, 3H), 6.84-6.81 (m, 4H), 6.13 (s, 1H), 4.82 (s, 2H), 3.77 (s, 3H), 3.77 (s, 3H), 3.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4, 158.1, 155.7, 148.8, 137.9, 132.1, 130.1, 129.8, 129.1, 128.7, 124.1, 118.1, 114.3, 113.9, 112.3, 55.4, 55.4, 47.8, 34.7; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.4; CH_2: 47.8, 34.7; CH_1: 130.1, 129.8, 129.1, 124.1, 118.1, 114.3, 113.9, 112.3; IR (neat): 2933, 2834, 1611, 1587, 1509, 1476, 1299, 1240, 1204, 1174, 1030, 807, 755, 687 cm^{-1}. HRMS (ESI) Calculated for $C_{25}H_{25}N_2O_3$ *m/z* (M+H) 401.1865, Obsd. 401.1860.



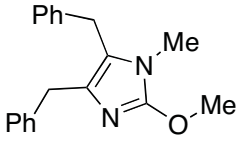
4,5-dibenzyl-1-methyl-2-phenoxy-1*H*-imidazole 3.8b. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2c** and phenol to give 2-oxoimidazole **3.8b** as a light-yellow oil in 76% yield. R_f = 0.34 (25%

acetone/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.12 (m, 11H), 7.10-7.06 (m, 2H), 7.05-7.02 (m, 2H), 3.91 (s, 2H), 3.88 (s, 2H), 3.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.0, 148.2, 141.1, 138.5, 133.1, 129.8, 128.8, 128.7, 128.4, 128.1, 126.6, 126.0, 123.8, 122.3, 117.4, 33.8, 29.7, 29.2; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 29.2; CH_2: 33.8, 29.7; CH_1: 129.8, 128.8, 128.7, 128.4, 128.1, 126.6, 126.0, 123.8, 117.4; CH_0: 156.0, 148.2, 141.1, 138.5, 133.1, 122.3; IR (neat): 3060, 3026, 2910, 1593, 1520, 1482, 1453, 1408, 1237, 1209, 1159, 1073, 1027, 750, 726, 695 cm^{-1}. HRMS (ESI) Calculated for $C_{24}H_{23}N_2O$ *m/z* (M+H) 355.1810, Obsd. 355.1807.



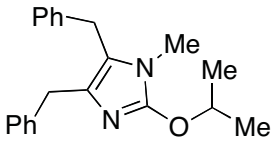
5 - (4 - (benzyloxy)benzyl) - 4 - (4 - methoxybenzyl) - 1 - methyl - 2 - phenoxy - 1*H* - imidazole 3.8c. Obtained from the base catalyzed addition-cyclization-isomerization reaction of cyanamide **3.2d** and phenol to give 2-oxoimidazole **3.8c**, as a light-yellow oil in 62% yield. R_f = 0.48 (40% EtOAc/hexane with 1% Et_3N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 9.0 Hz, 2H), 7.34-7.30 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 7.5 Hz, 2H), 6.79 (d, *J* = 9.5 Hz, 2H), 5.03 (s, 2H), 3.82 (s, 2H), 3.83 (s, 2H), 3.77 (s, 3H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.0, 157.7, 156.1, 148.2, 137.2, 133.4, 133.3, 130.9, 129.8, 129.7, 129.2, 128.8, 128.2, 127.7, 123.8, 122.5, 117.5, 115.2, 113.9, 70.3, 55.5, 33.0, 29.3, 28.9; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.5, 29.3; CH_2: 70.3, 33.0, 28.9; CH_1: 129.8, 129.7, 129.2, 128.8, 128.2, 127.7, 123.8, 117.5, 115.2, 113.9; CH_0: 158.0, 157.7, 156.1, 148.2, 137.2, 133.4, 133.3, 130.9, 122.5.

IR (neat): 3032, 2932, 1609, 1509, 1486, 1242, 1026, 754 cm^{-1}. HRMS (ESI) Calculated for $C_{32}H_{31}N_2O_3$ *m/z* (M+H) 491.2335, Obsd. 491.2329.



4,5-dibenzyl-2-methoxy-1-methyl-1*H*-imidazole 3.9a. In a 15 mL high-pressure tube containing a magnetic stir bar was added cyanamide **3.2c** (0.113 g, 0.435 mmol, 1.0 equiv.), K_2CO_3 (0.601 g, 4.35 mmol, 10.0 equiv.) and methanol (4.0 mL). The high-pressure tube was then sealed and placed in a preheated 150 °C oil bath. After 24 h at 150 °C, the high-pressure was removed from the oil bath and left to cool to rt. The crude reaction mixture was diluted in CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 2.5 × 15 cm column, eluting with 400 mL of 20% EtOAc/hexanes (with 1% Et_3N). The product containing fractions were combined and then concentrated under reduced pressure to give 2-oxoimidazole **3.9a** (0.1041 g, 82% yield) as a light yellow oil. R_f = 0.18 (35% EtOAc/hexane, 1% Et_3N). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.18 (m, 6H), 7.17-7.11 (m, 2H), 7.03-7.00 (m, 2H), 3.99 (s, 3H), 3.88 (s, 2H), 3.81 (s, 2H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.5, 141.3, 138.9, 131.4, 128.6, 128.6, 128.3, 128.1, 126.4, 125.9, 121.2, 56.4, 33.7, 29.6, 28.4; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 56.4, 28.4; CH2: 33.7, 29.6; CH_1: 128.6, 128.6, 128.3, 128.1, 126.4, 125.9; CH_0: 152.5, 141.3, 138.9, 131.4, 121.2; IR (neat): 3025, 2940, 1602, 1547, 1505, 1493, 1452, 1409, 1376, 1195, 1139, 1024, 725, 695 cm^{-1}. HRMS (ESI) Calculated for $C_{19}H_{21}N_2O$

m/z (M+H) 293.1654, Obsd. 293.1650.



4,5-dibenzyl-2-isopropoxy-1-methyl-1*H*-imidazole 3.9b. In a 15 mL high-pressure tube containing a magnetic stir bar was added cyanamide **3.2c** (0.1030 g, 0.396 mmol, 1.0 equiv.), K_2CO_3 (0.5468 g, 3.96 mmol, 10.0 equiv.) and methanol (4.0 mL). The high-pressure tube was then sealed and placed in a preheated 150 °C oil bath. After 24 h at 150 °C, the high-pressure was removed from the oil bath and left to cool to rt. The crude reaction mixture was diluted in CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 2.5 ´ 15 cm column, eluting with 300 mL of 20% EtOAc/hexanes (with 1% Et_3N). The product containing fractions were combined and then concentrated under reduced pressure to give 2-oxoimidazole **3.9b** (0.0854 g, 67% yield) as a light yellow oil. R_f = 0.45 (35% EtOAc/hexane, 1% Et_3N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.24 (m, 2H), 7.23-7.18 (m, 4H), 7.17-7.10 (m, 2H), 7.03-6.99 (m, 2H), 5.09 (sept, *J* = 6.2 Hz, 1H), 3.87 (s, 2H), 3.79 (s, 2H), 3.01 (s, 3H), 1.33 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.5, 141.5, 139.1, 131.4, (2 × 128.6) 128.3, 128.2, 126.4, 125.8, 120.6, 72.5, 33.7, 29.6, 28.4, 22.4; ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 28.4, 22.4; CH_2: 33.7, 29.6; CH_1: (2 × 128.6), 128.3, 128.2, 126.4, 125.8, 72.5; CH_0: 151.5, 141.5, 139.1, 131.4, 120.6; IR (neat): 3061, 3026, 2977, 2932, 1735, 1649, 1602, 1532, 1493, 1452,

1409, 1383, 1108, 975, 724, 695 cm^{-1}. HRMS (ESI) Calculated for $C_{21}H_{25}N_2O$ *m/z* (M+H) 321.1967, Obsd. 321.1964.

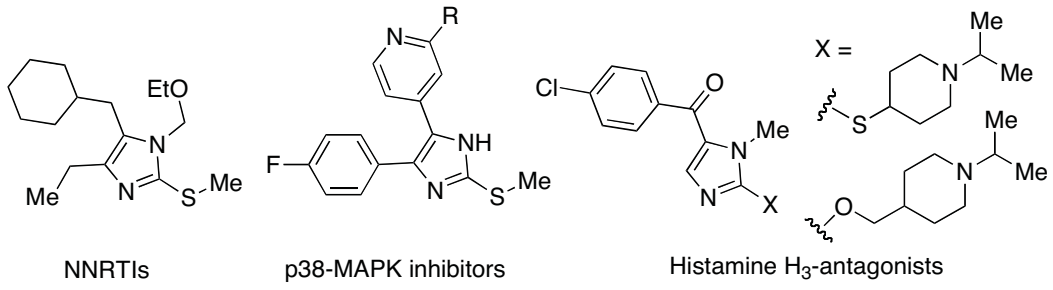


Figure 3.1. Medicinally relevant 2-thio and 2-oxoimidazoles

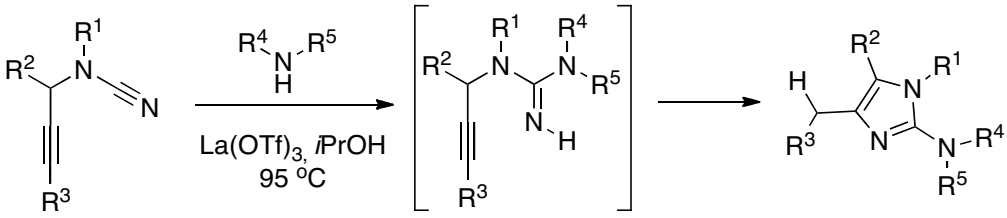
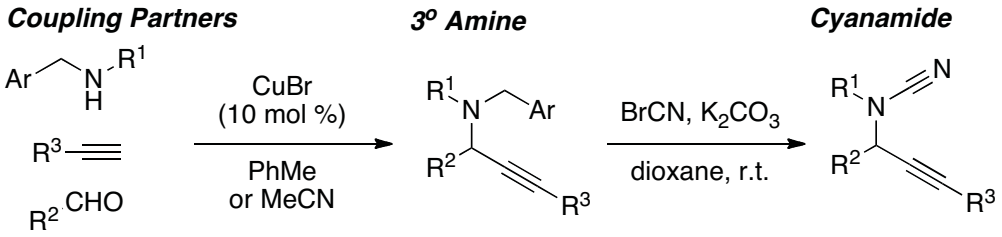
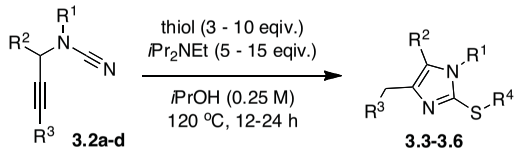


Figure 3.2. Addition-hydroamination-isomerization sequence.



Coupling Partners	3º Amine	Cyanamide
PMB_2NH, PMP—≡, HCHO	**3.1a**, 98%	**3.2a**, 94%
PMBNHBn, Ph—≡, HCHO	**3.1b**, 90%	**3.2b**, 90%
PMBNHMe, Ph—≡, $PhCH_2CHO$	**3.1c**, 94%	**3.2c**, 87%
PMBNHMe, PMP—≡, 4-$BnOPhCH_2CHO$	**3.1d**, 98%	**3.2d**, 76%

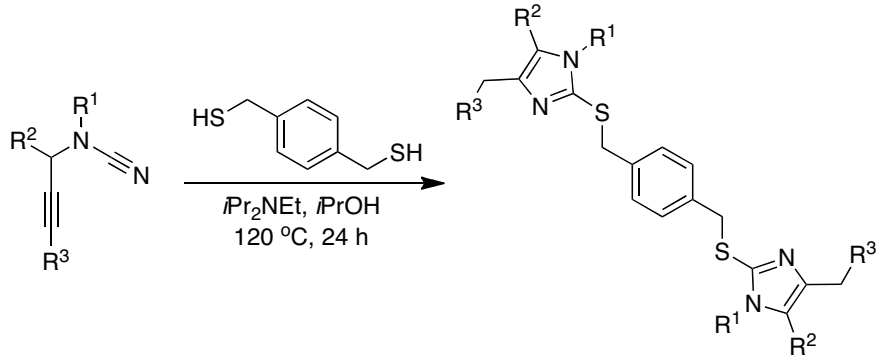
Figure 3.3. Synthesis of propargylcyanamides.



3.2a-d **3.3-3.6**

Entry	cyanamide	thiol	2-thioimidazole	R^1	R^2	R^3	Yield
1	**3.2a**	Me–SH	**3.3a**	PMB	H	PMP	67%
2	**3.2b**		**3.3b**	Bn	H	Ph	77%
3	**3.2c**		**3.3c**	Me	Bn	Ph	93%
4	**3.2d**		**3.3d**	Me	*p*-BnOBn	PMP	82%
5	**3.2a**	MeO–SH	**3.4a**	PMB	H	PMP	67%
6	**3.2b**		**3.4b**	Bn	H	Ph	77%
7	**3.2c**		**3.4c**	Me	Bn	Ph	93%
8	**3.2d**		**3.4d**	Me	*p*-BnOBn	PMP	82%
9	**3.2a**	SH	**3.5a**	PMB	H	PMP	67%
10	**3.2b**		**3.5b**	Bn	H	Ph	77%
11	**3.2c**		**3.5c**	Me	Bn	Ph	93%
12	**3.2d**		**3.5d**	Me	*p*-BnOBn	PMP	82%
13	**3.2a**	HO–SH	**3.6a**	PMB	H	PMP	67%
14	**3.2b**		**3.6b**	Bn	H	Ph	77%
15	**3.2c**		**3.6c**	Me	Bn	Ph	93%
16	**3.2d**		**3.6d**	Me	*p*-BnOBn	PMP	82%

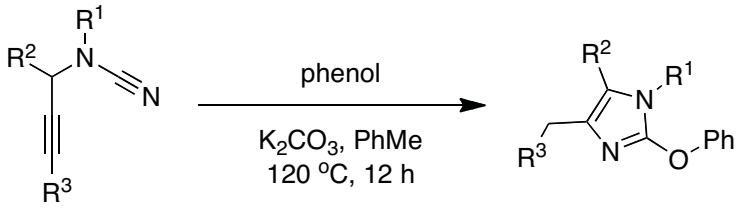
Figure 3.4. Synthesis of 2-thioimidazoles.



3.2b, R^1 = Bn, R^2 = H, R^3 = Ph
3.2c, R^1 = Me, R^2 = Bn, R^3 = Ph

3.7a, R^1 = Bn, R^2 = H, R^3 = Ph (71%)
3.7b, R^1 = Me, R^2 = Bn, R^3 = Ph (73%)

Figure 3.5. Synthesis of Bis-2-thioimidazoles.



3.2 **3.8**

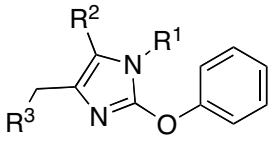
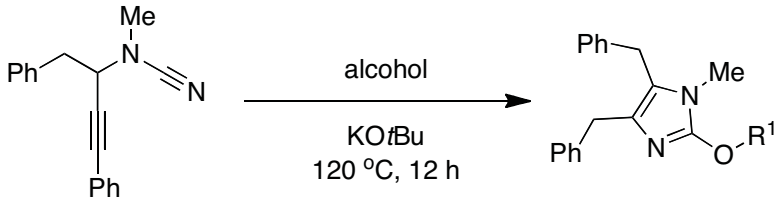
Entry	cyanamide	2-oxoimidazole				Yield
						
			R^1	R^2	R^3	
1	**3.2a**	**3.8a**	PMB	H	PMP	77%
2	**3.2c**	**3.8b**	Me	Bn	Ph	76%
3	**3.2d**	**3.8c**	Me	*p*-BnOBn	PMP	62%

Figure 3.6. Synthesis of 2-oxoimidazoles with phenol.



3.2c **3.9**

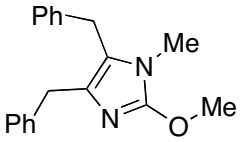
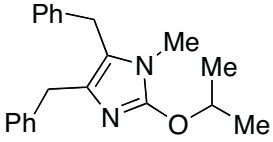
Entry	alcohol	2-oxoimidazole	Yield
1	MeOH	**3.9a** 	72%
2	*i*PrOH	**3.9b** 	67%

Figure 3.7. Synthesis of 2-oxoimidazoles with alcohols.

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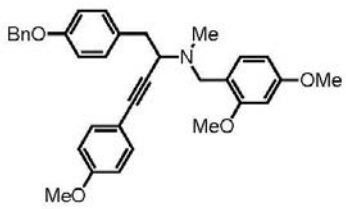
APPENDIX A

^{1}H, ^{13}C AND ^{13}C DEPT SPECTRA CHAPTER 2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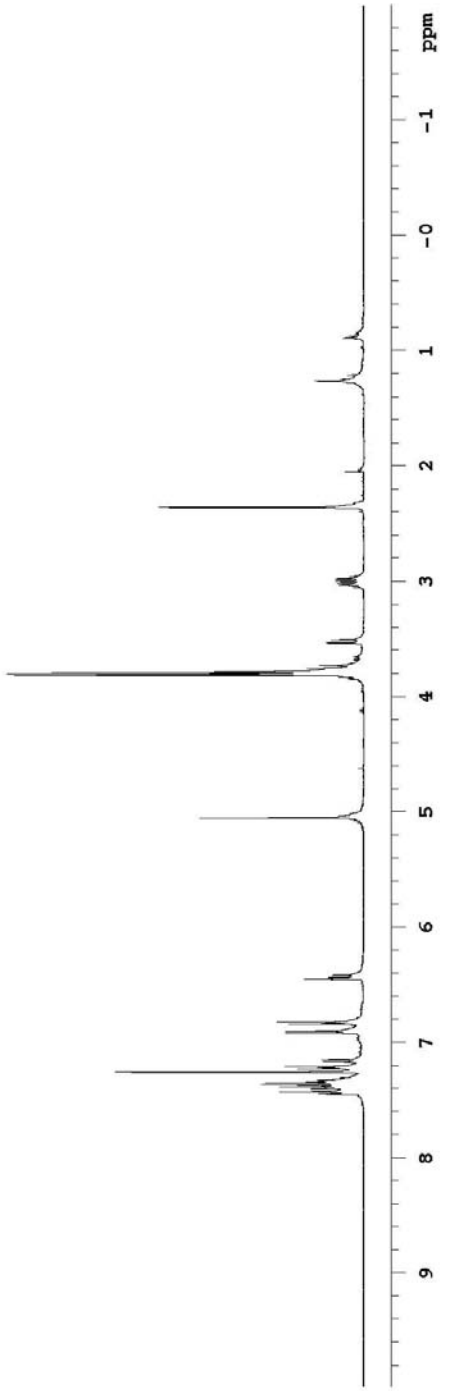
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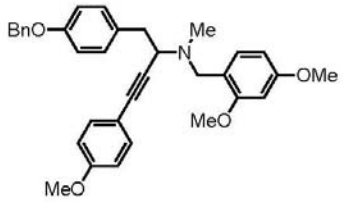
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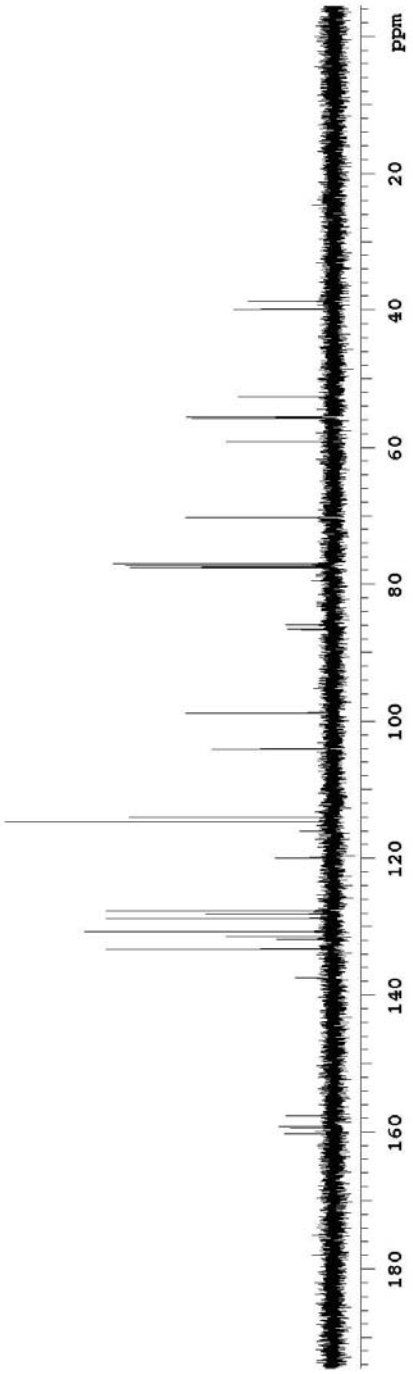
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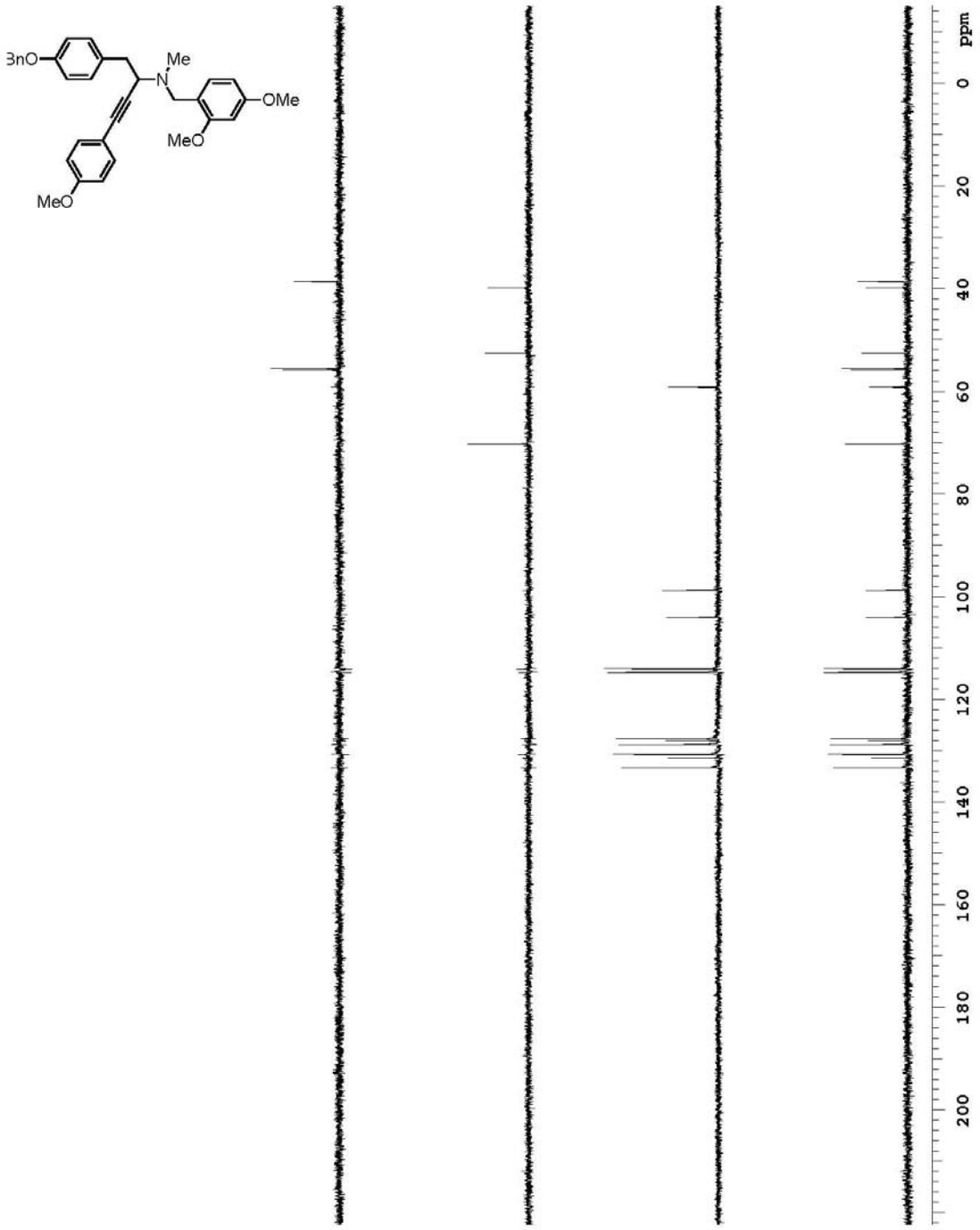
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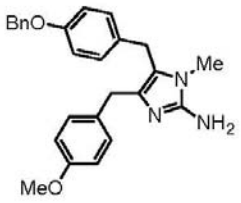
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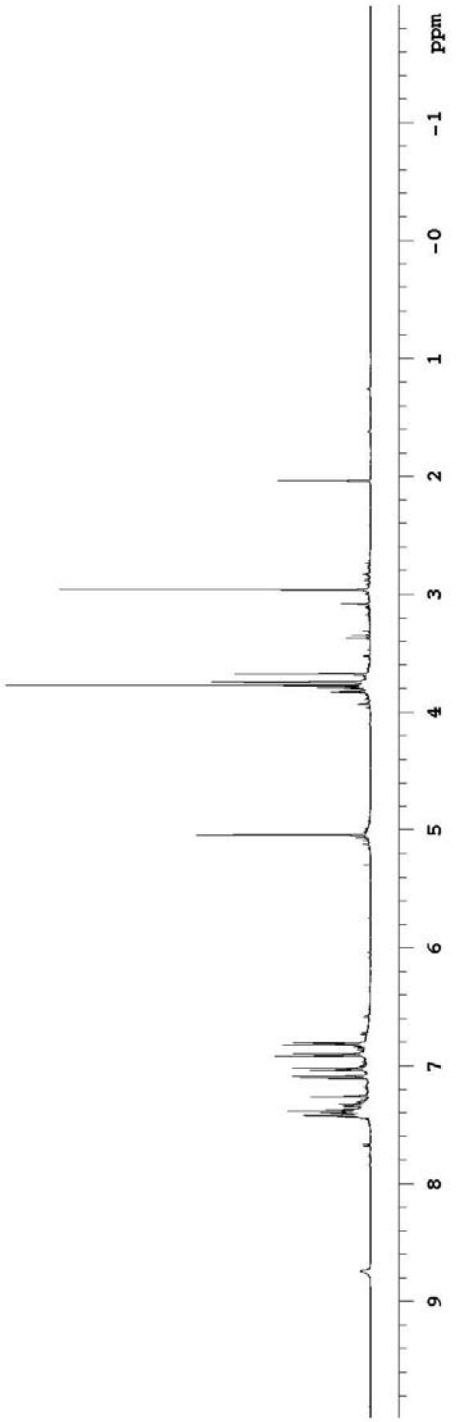
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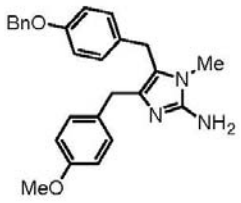
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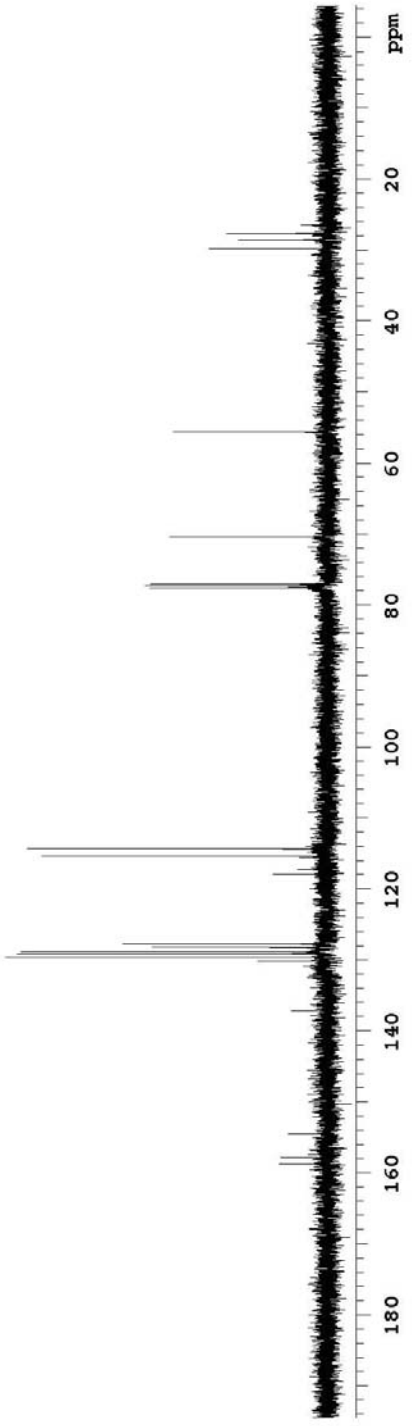
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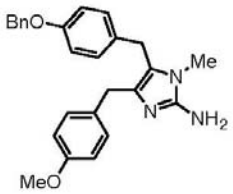
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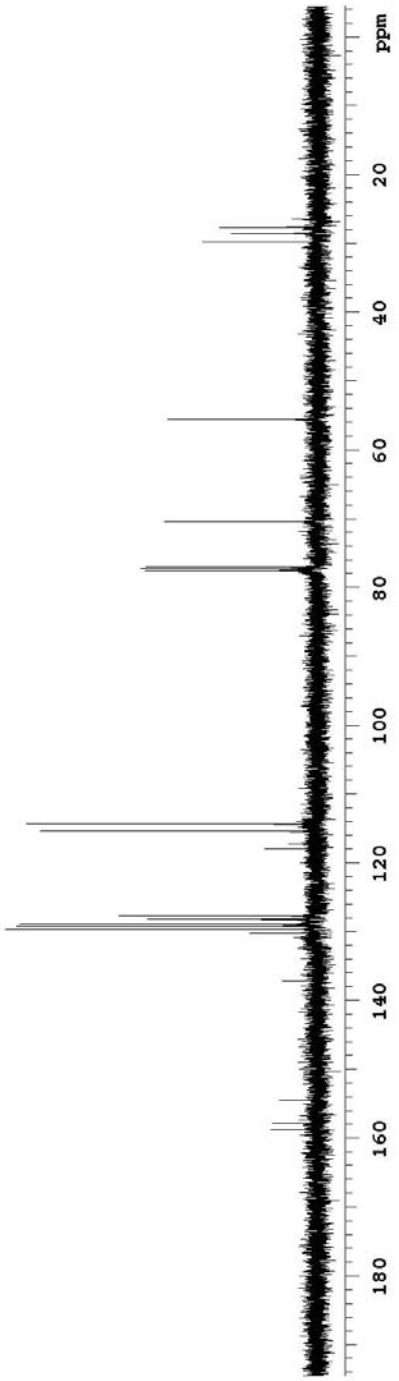
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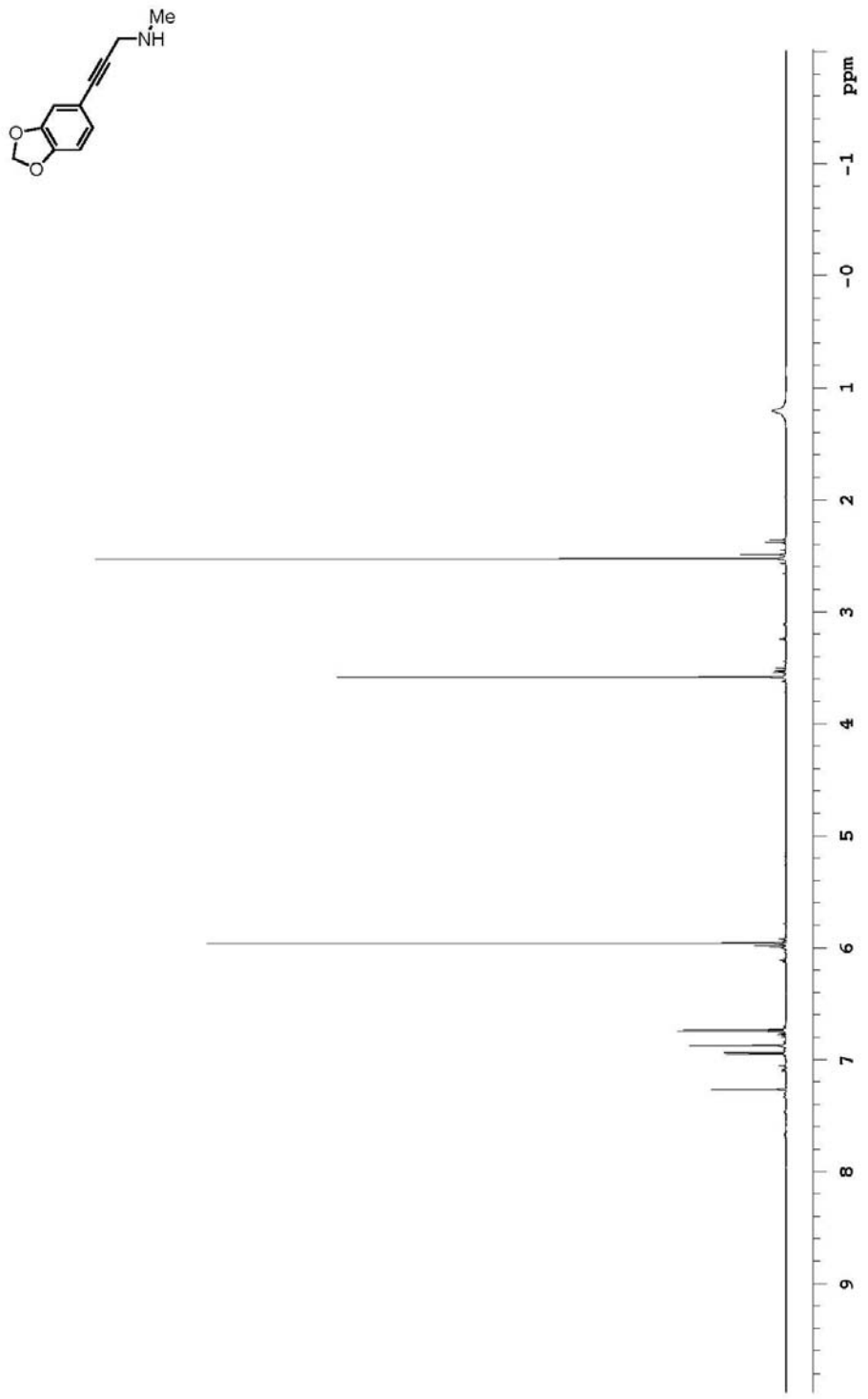
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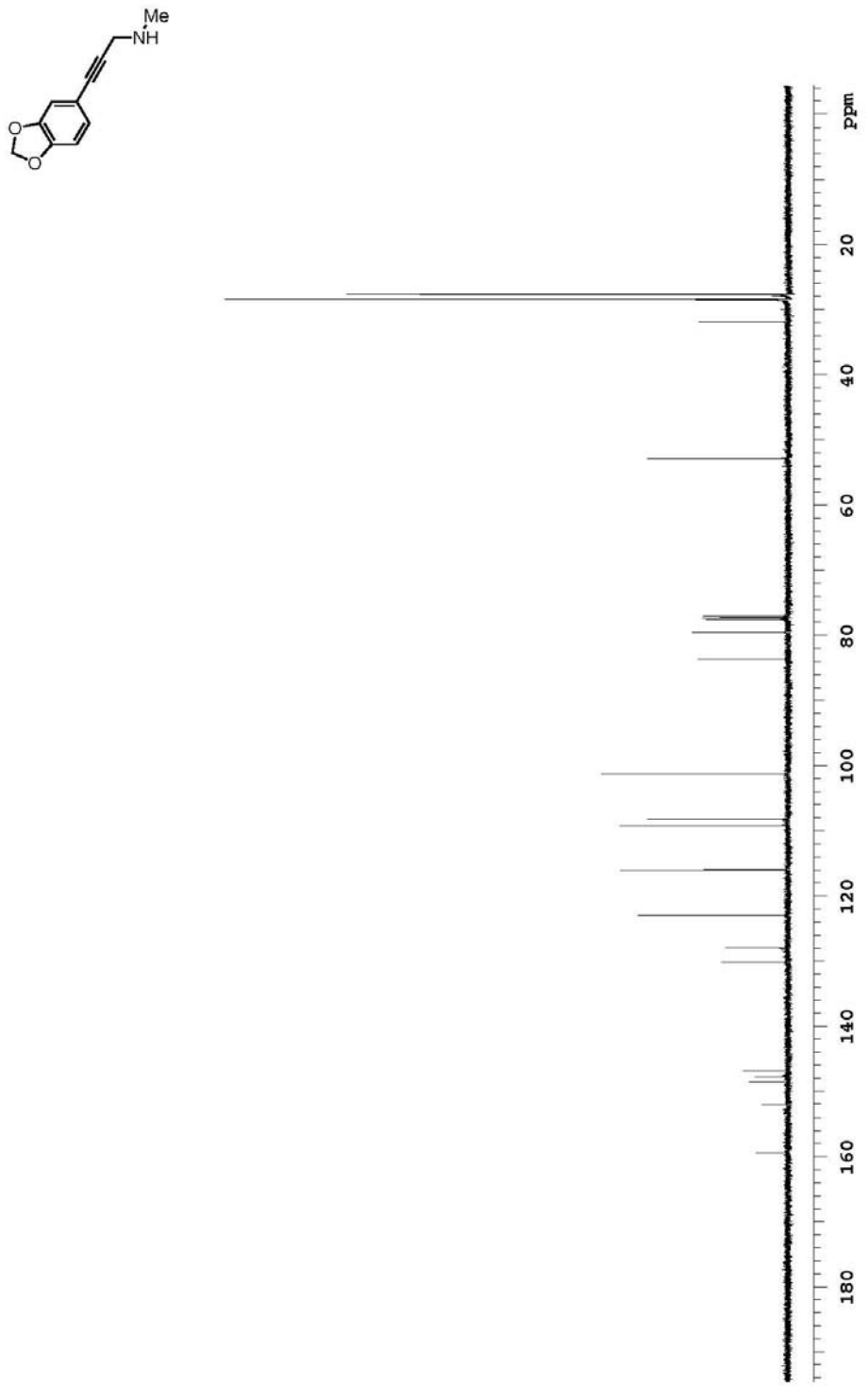
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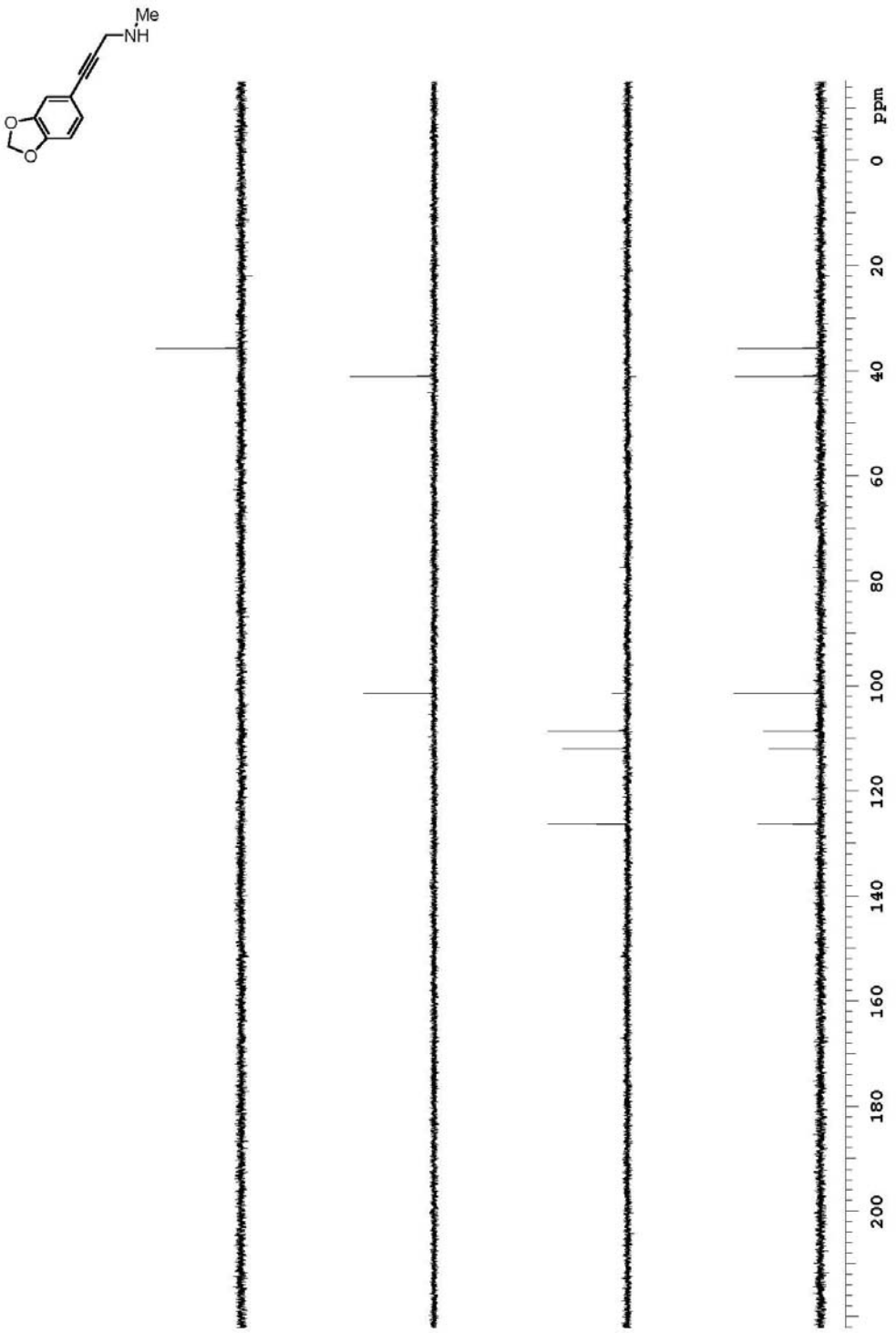
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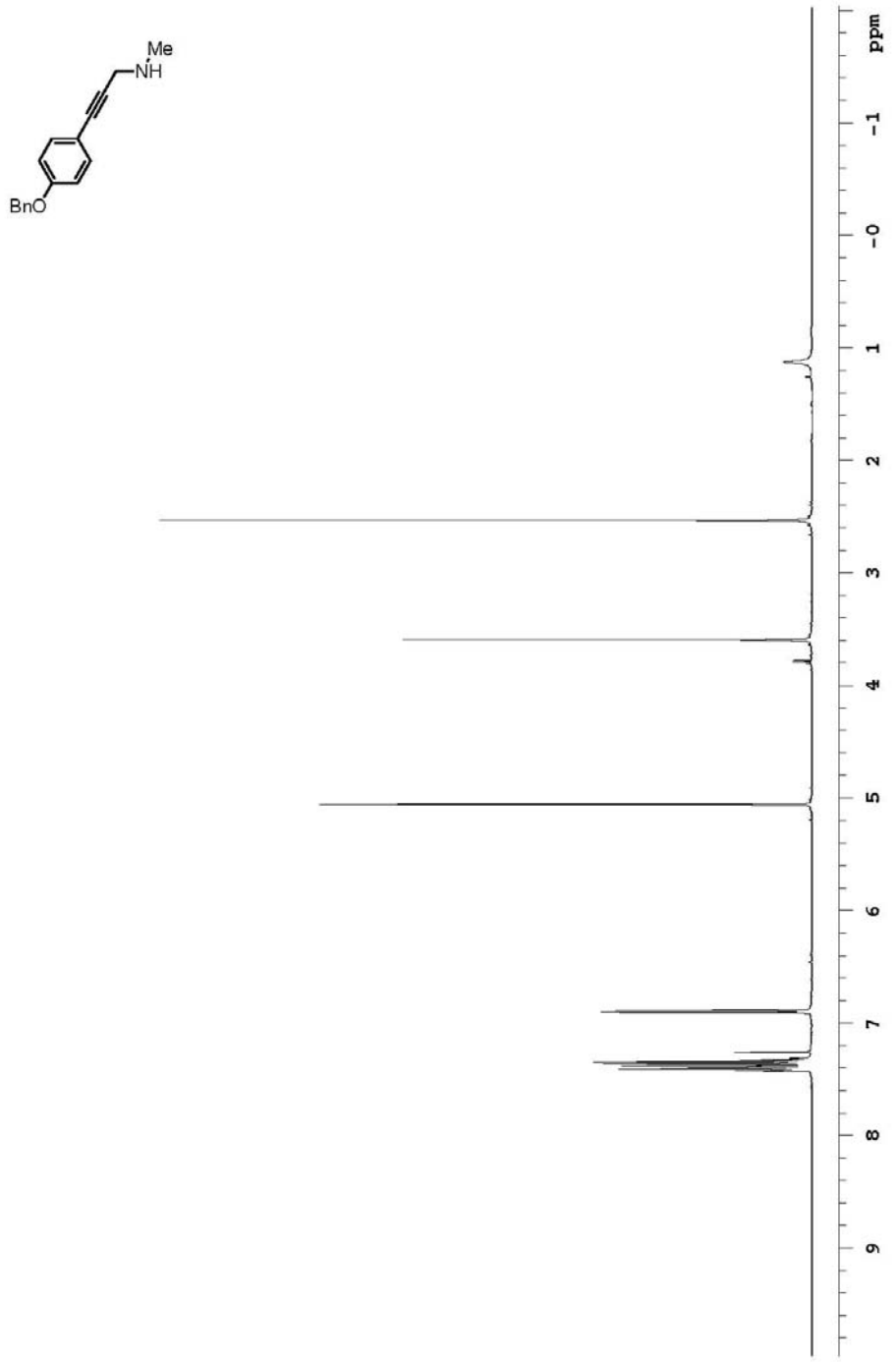
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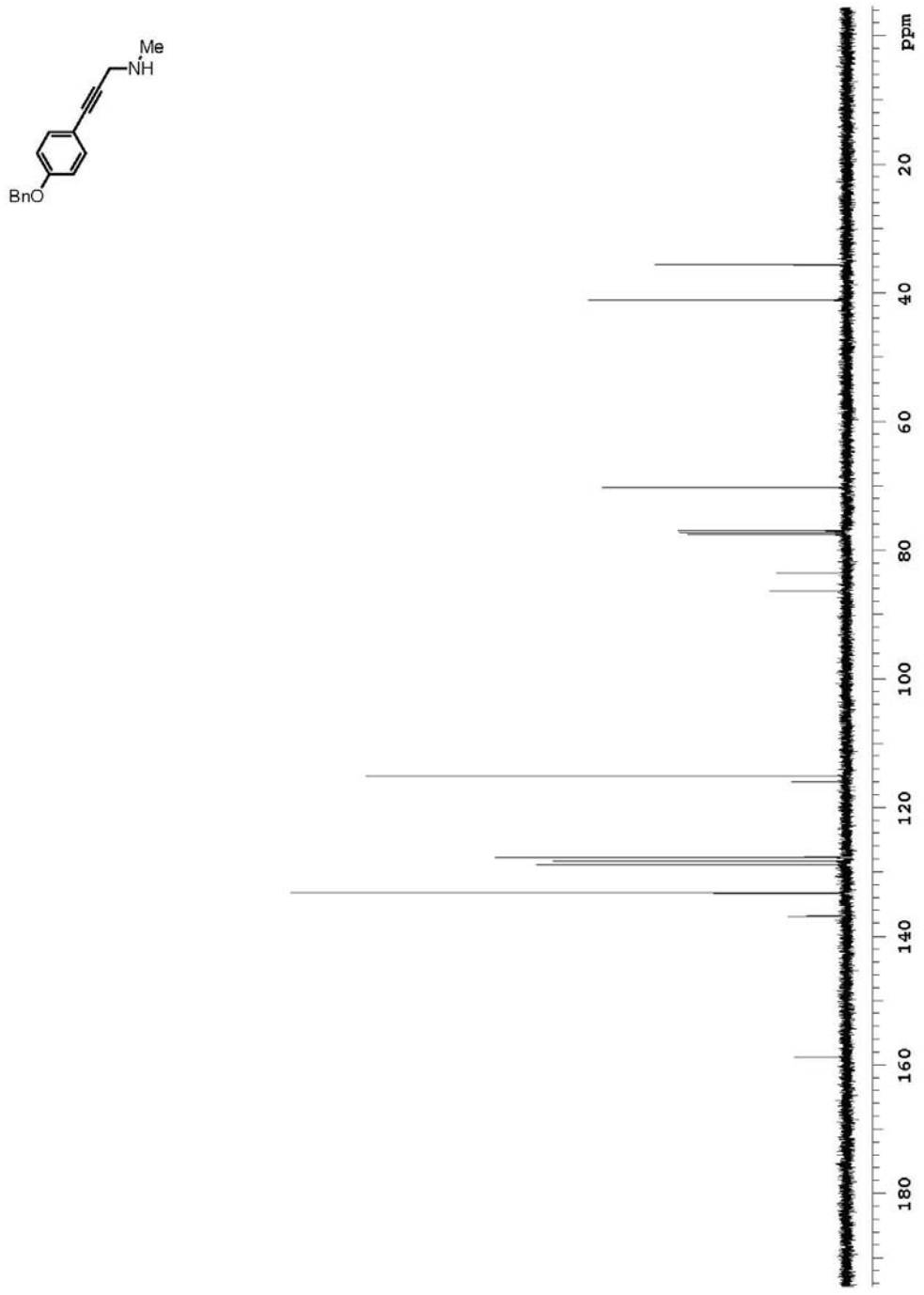
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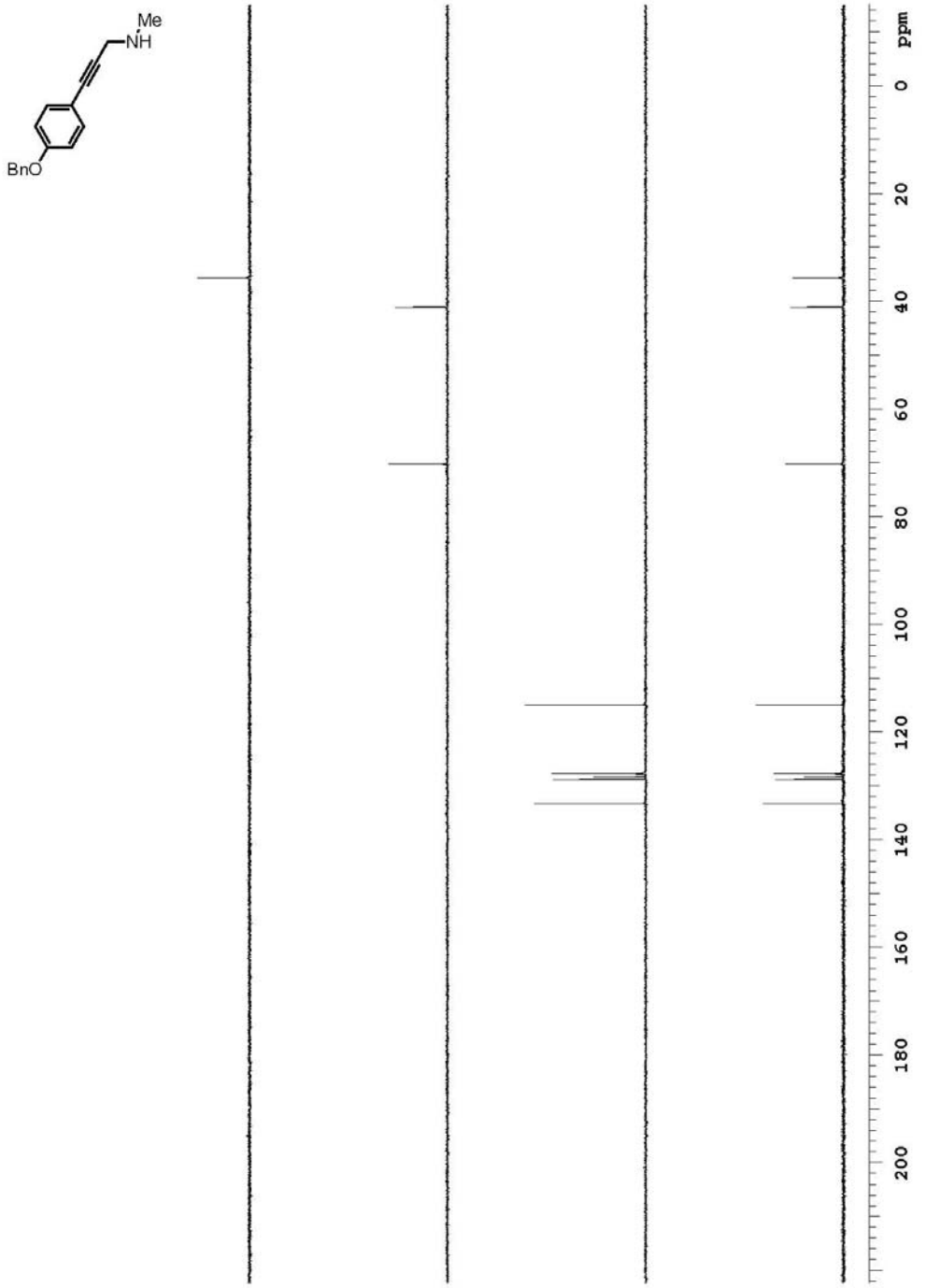
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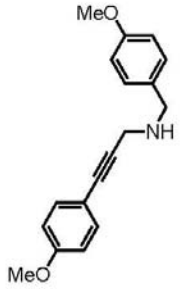
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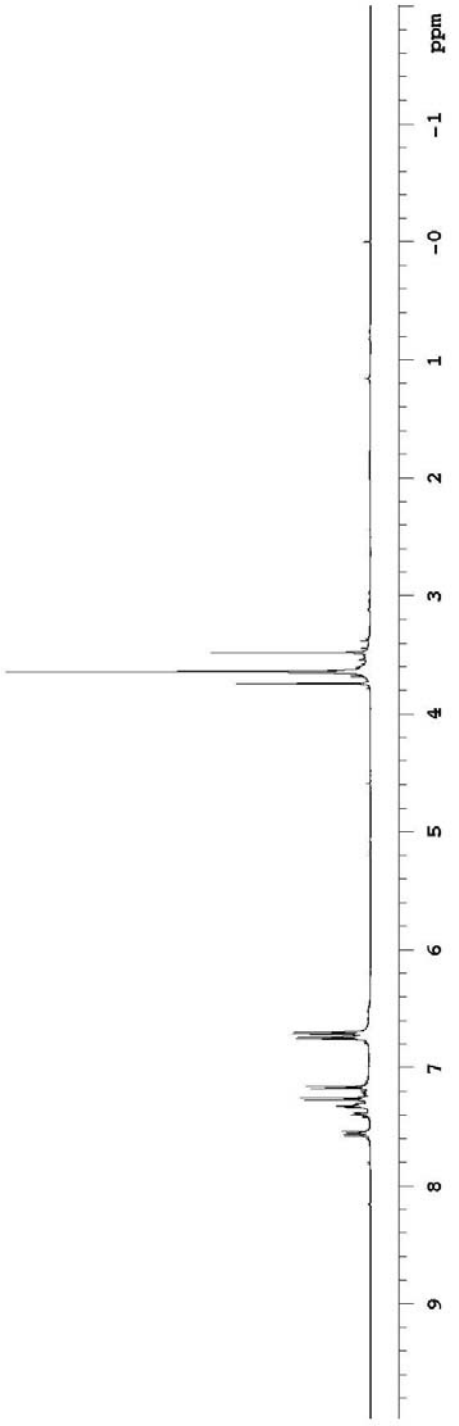
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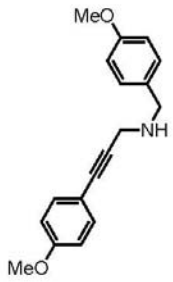
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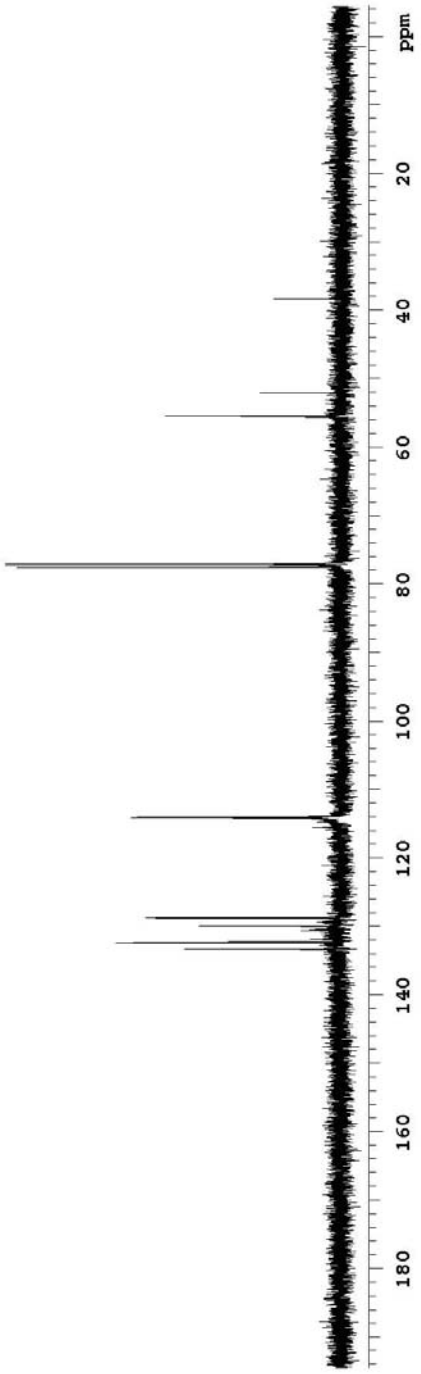
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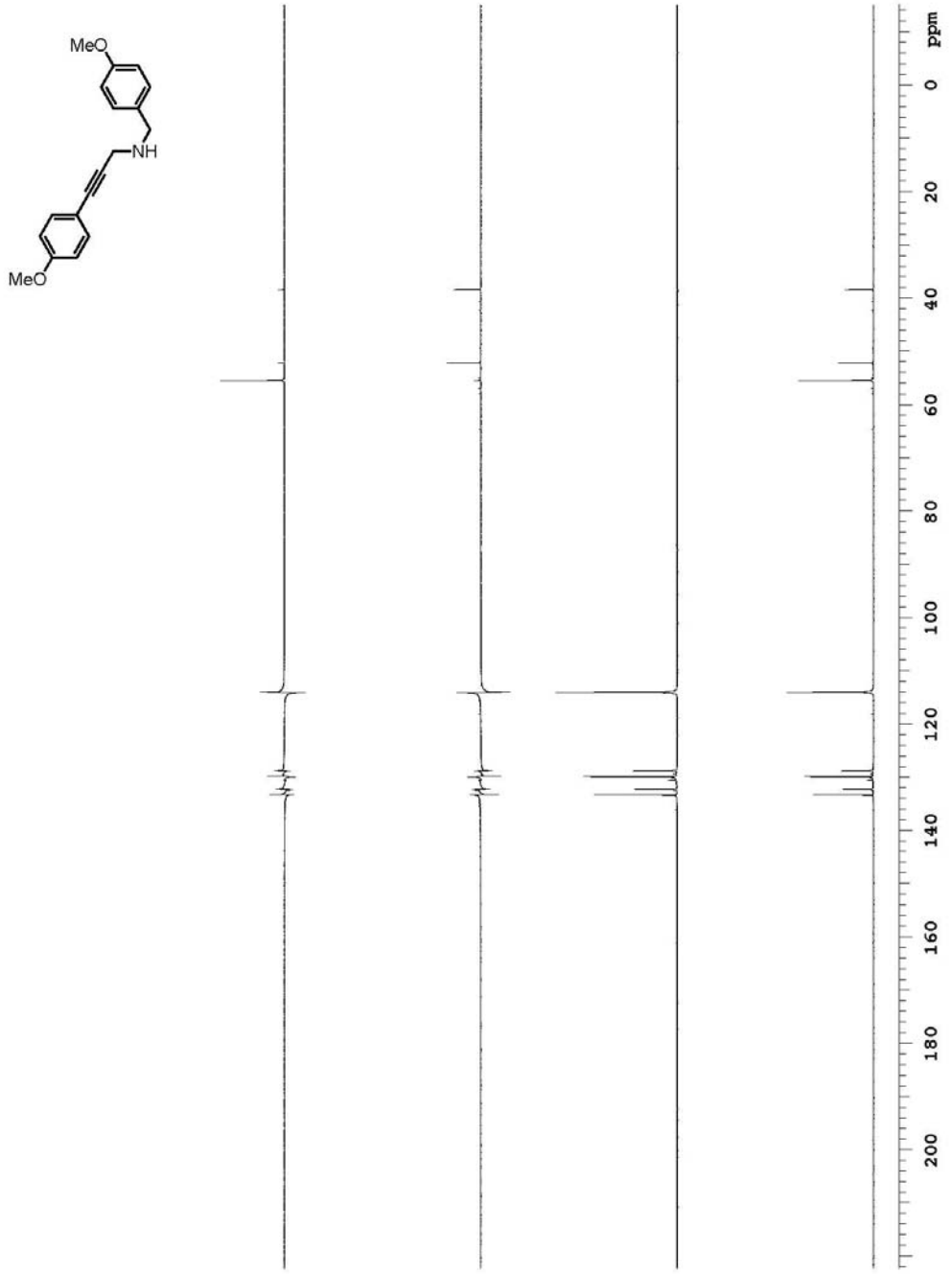
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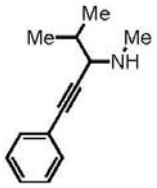
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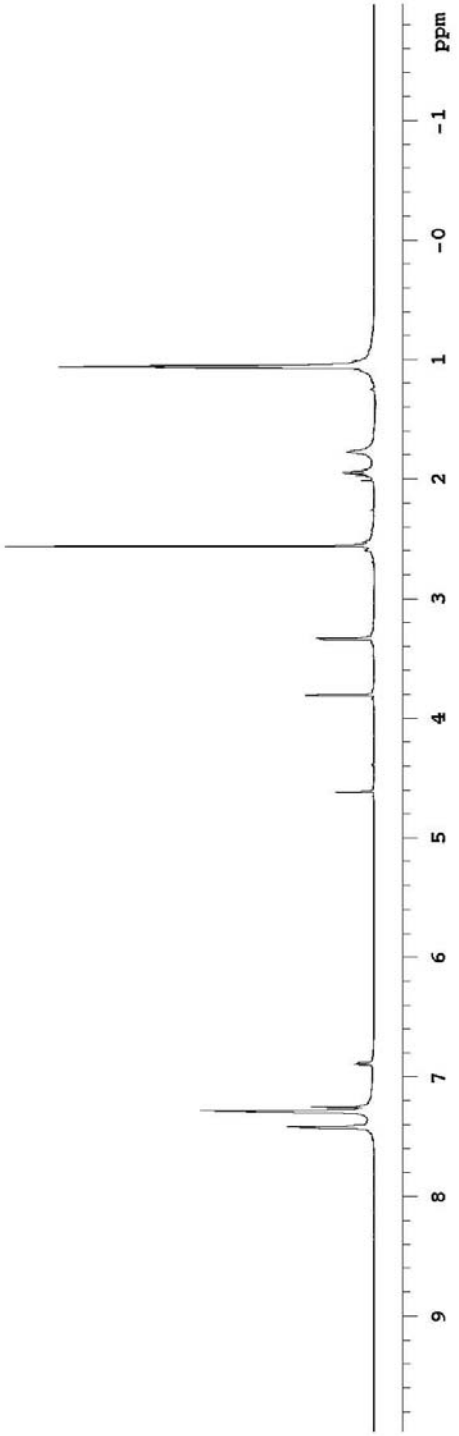
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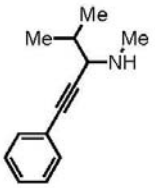
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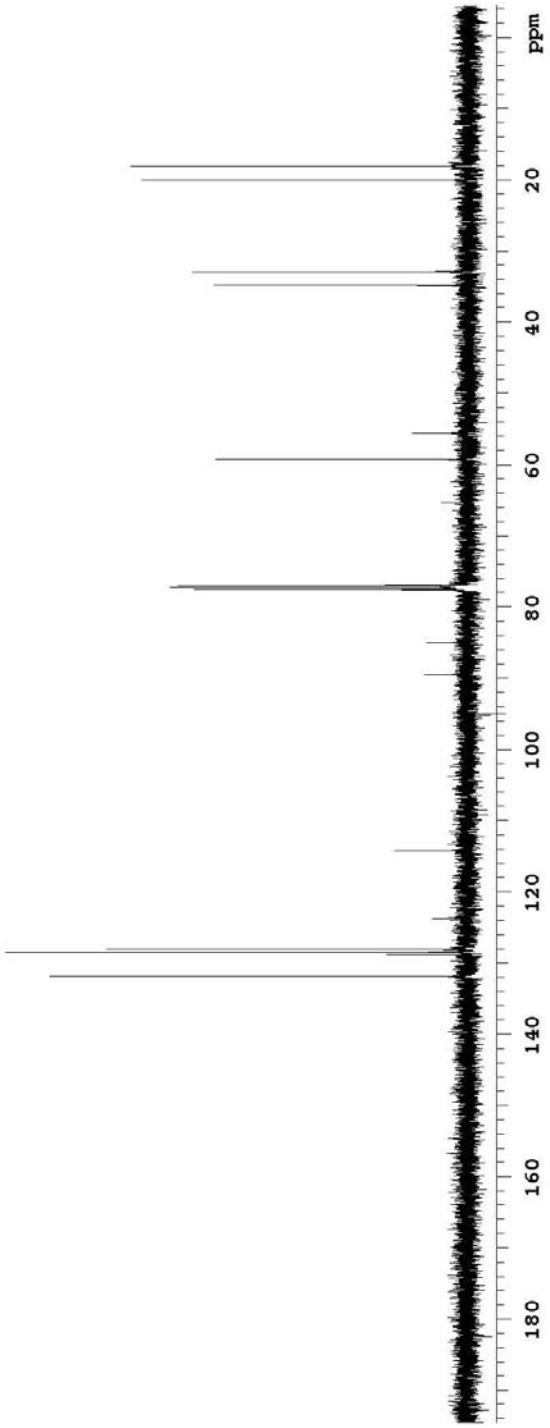
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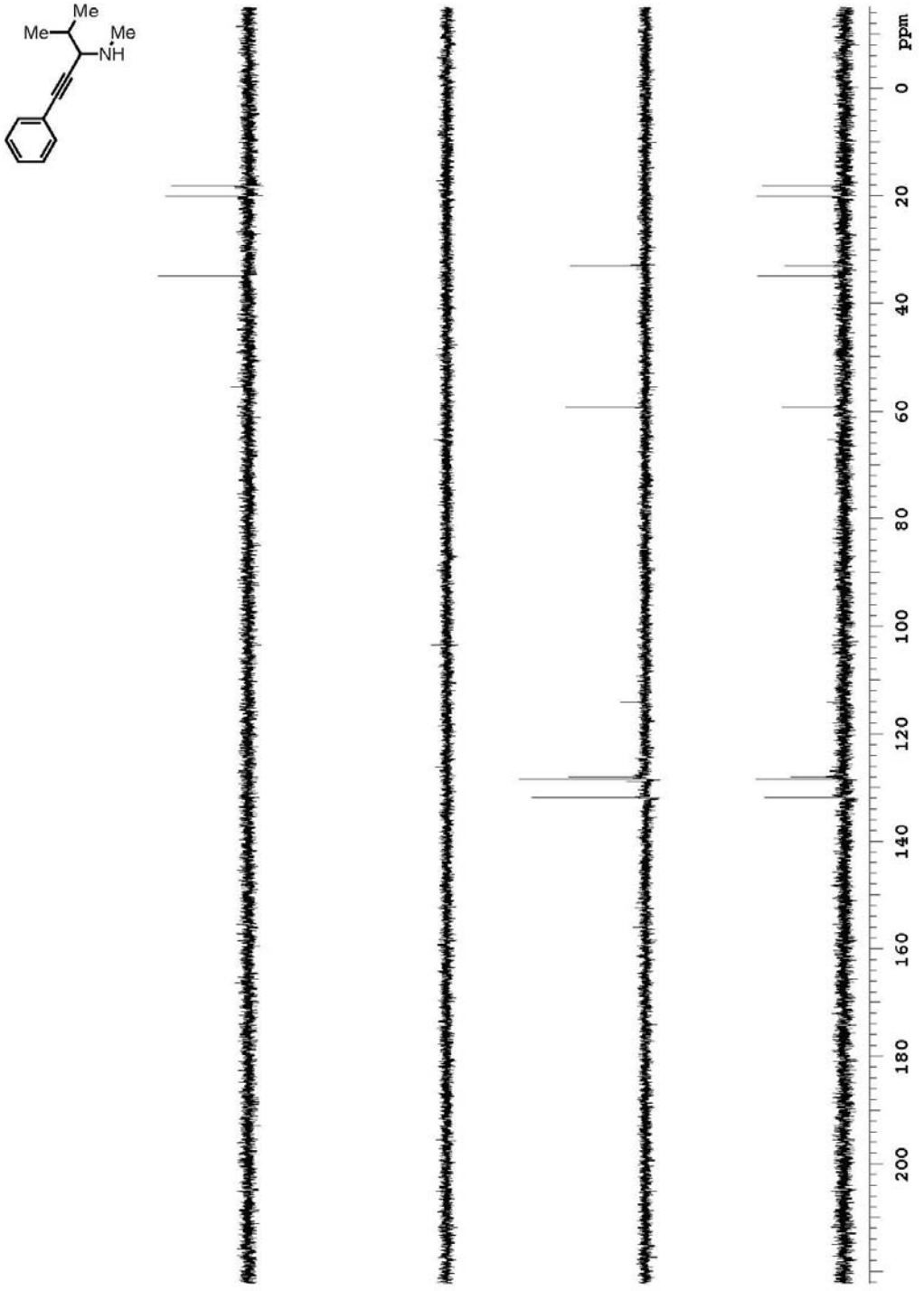
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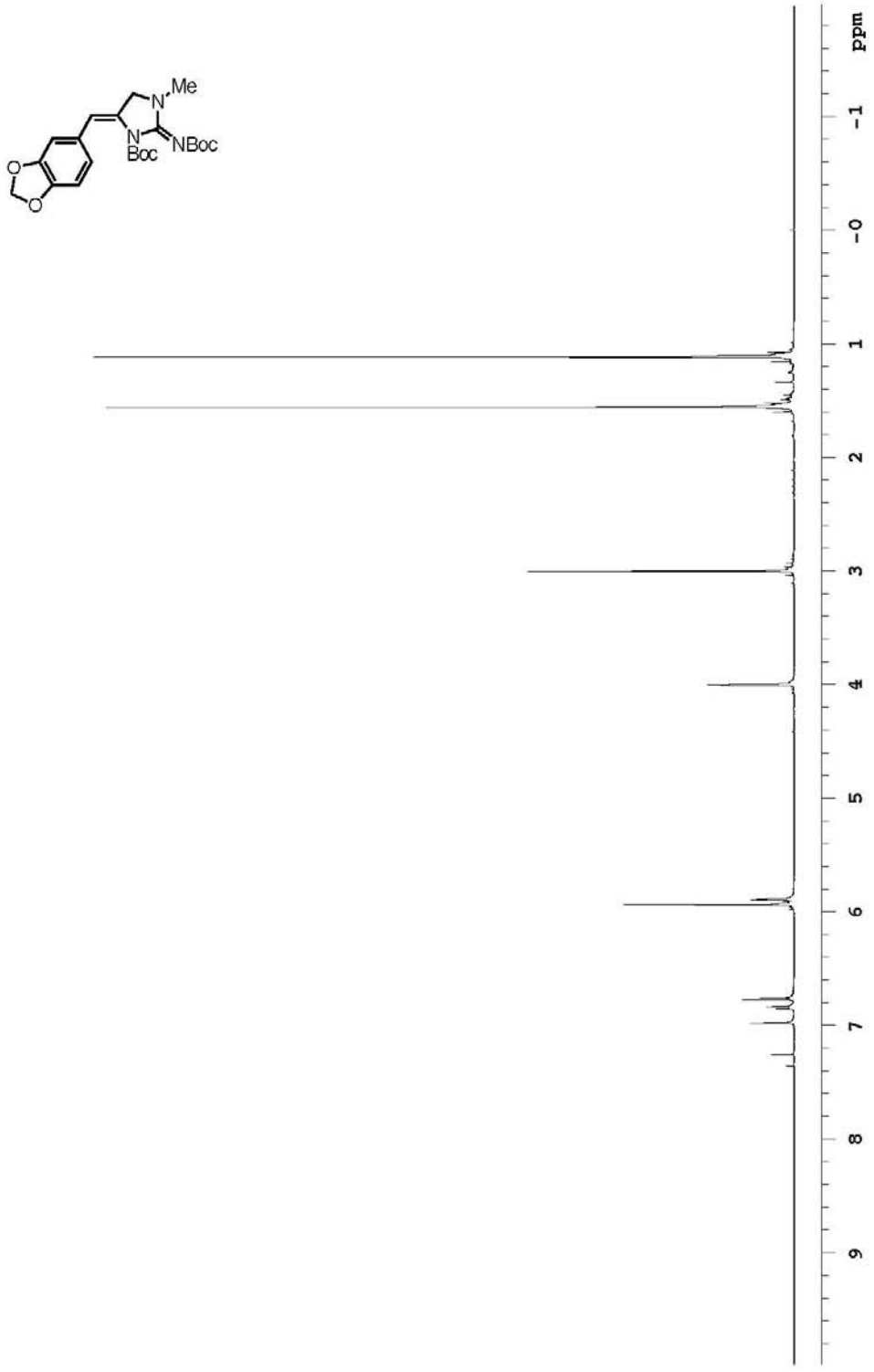
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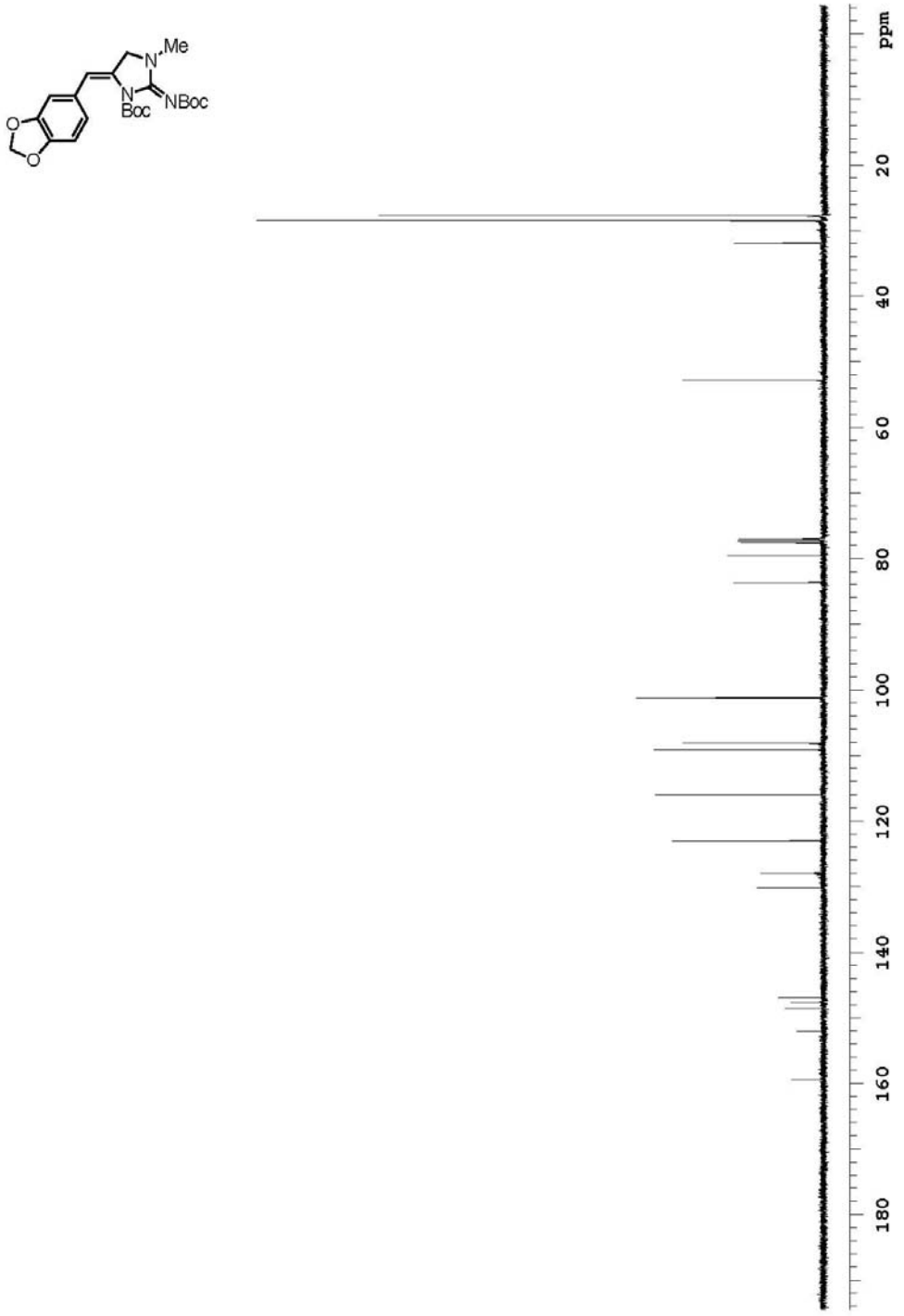
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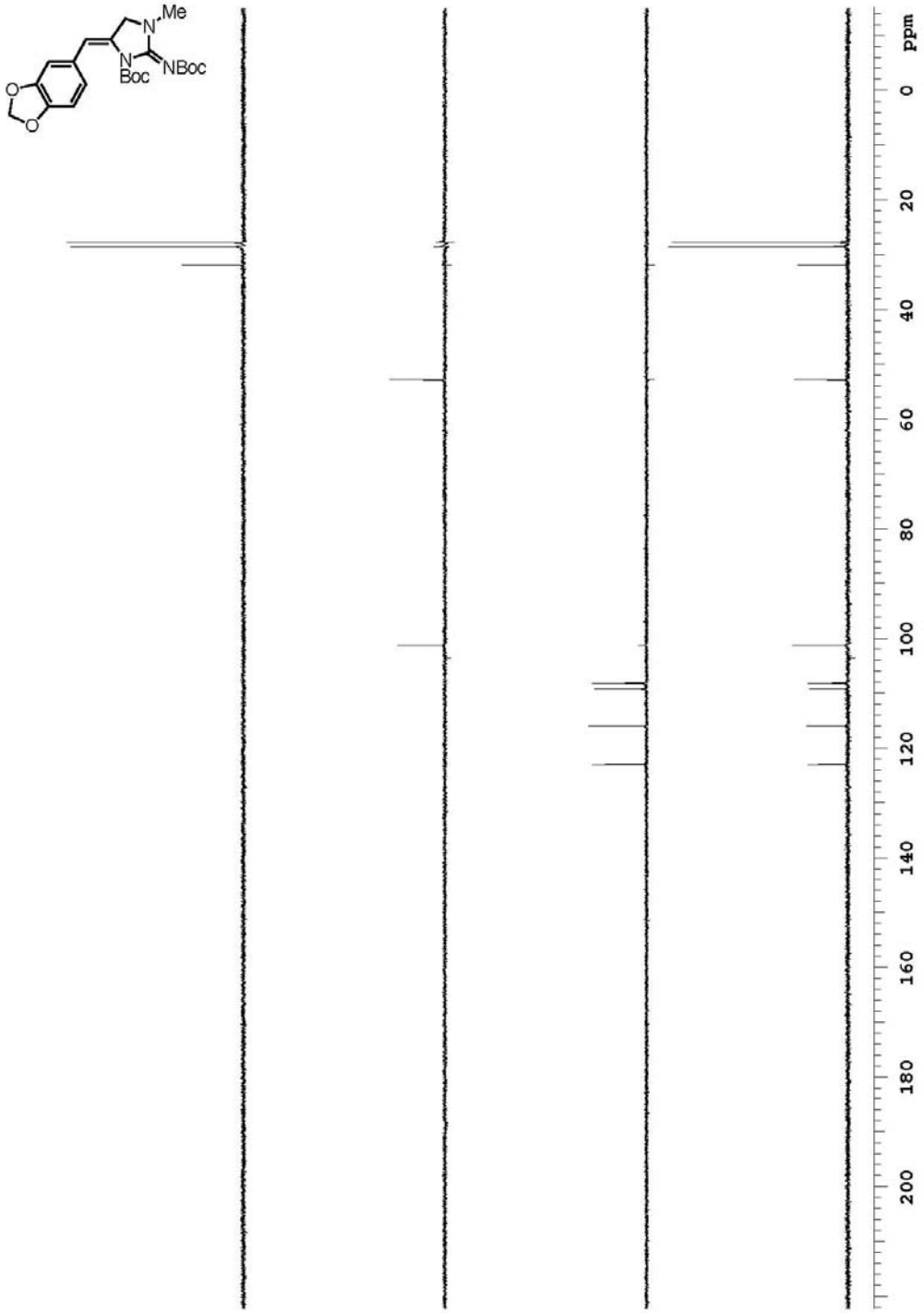
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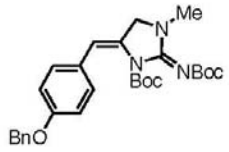
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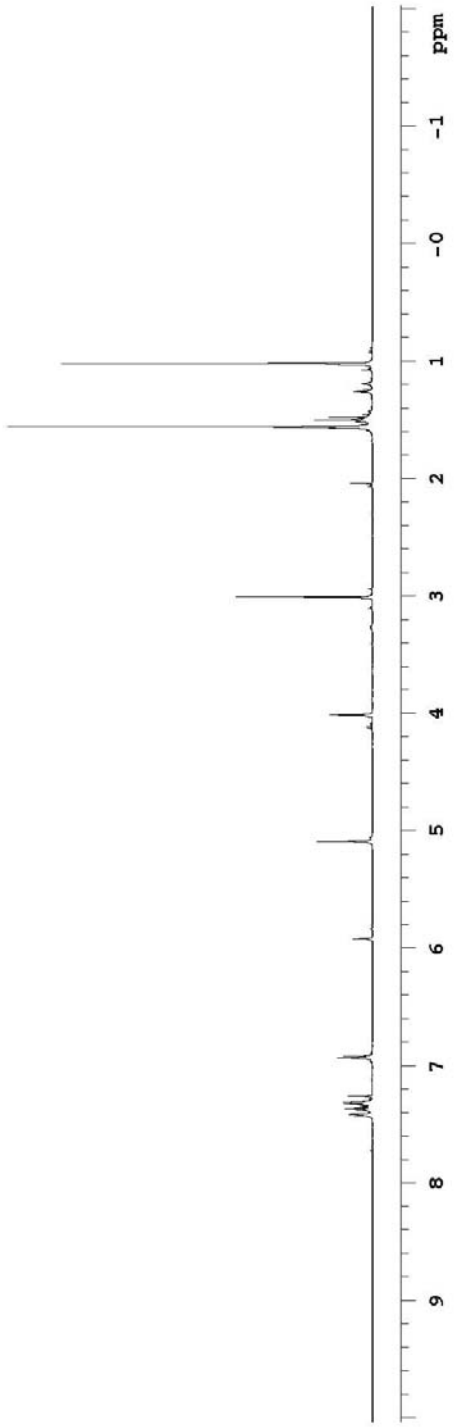
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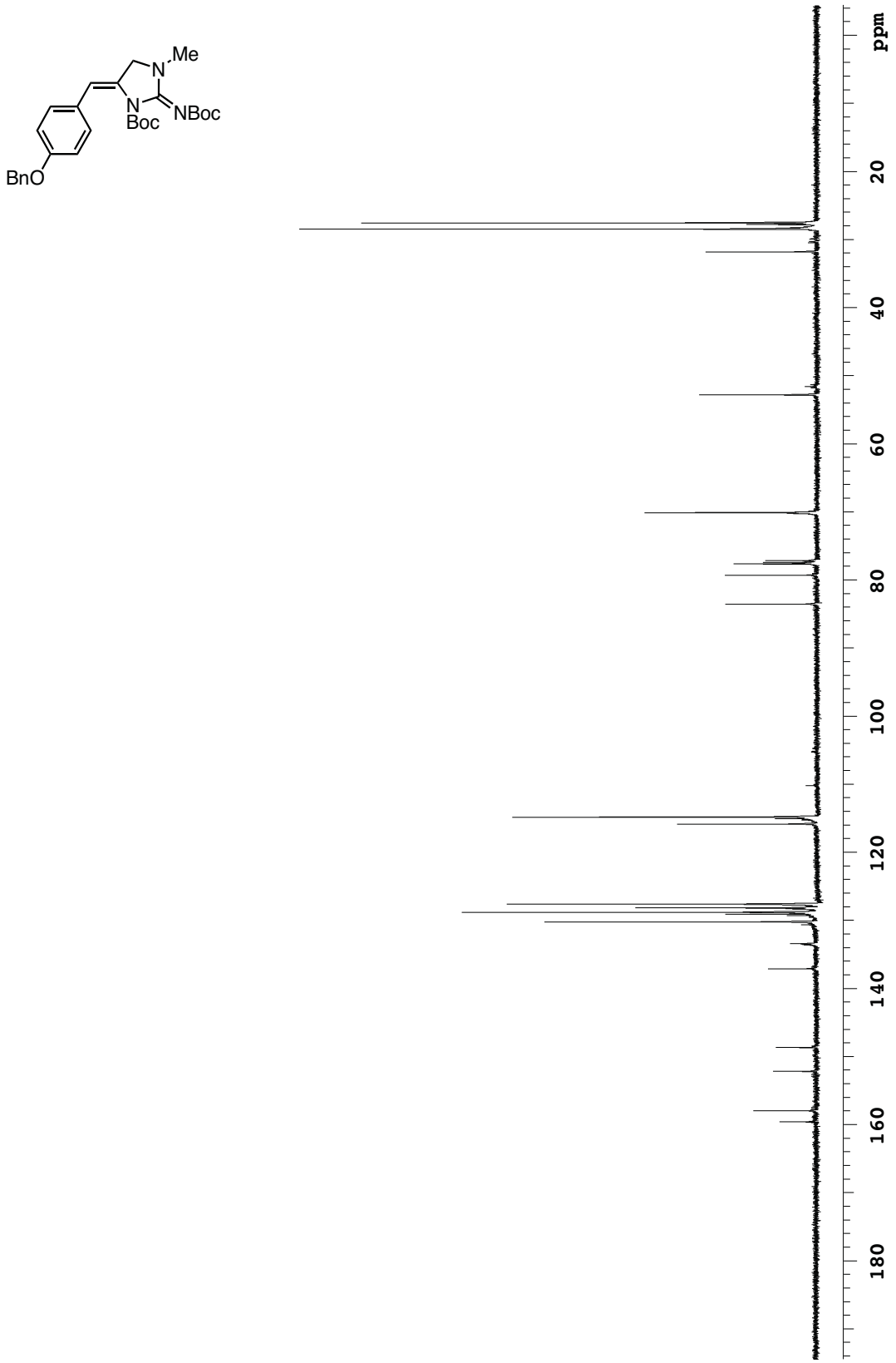
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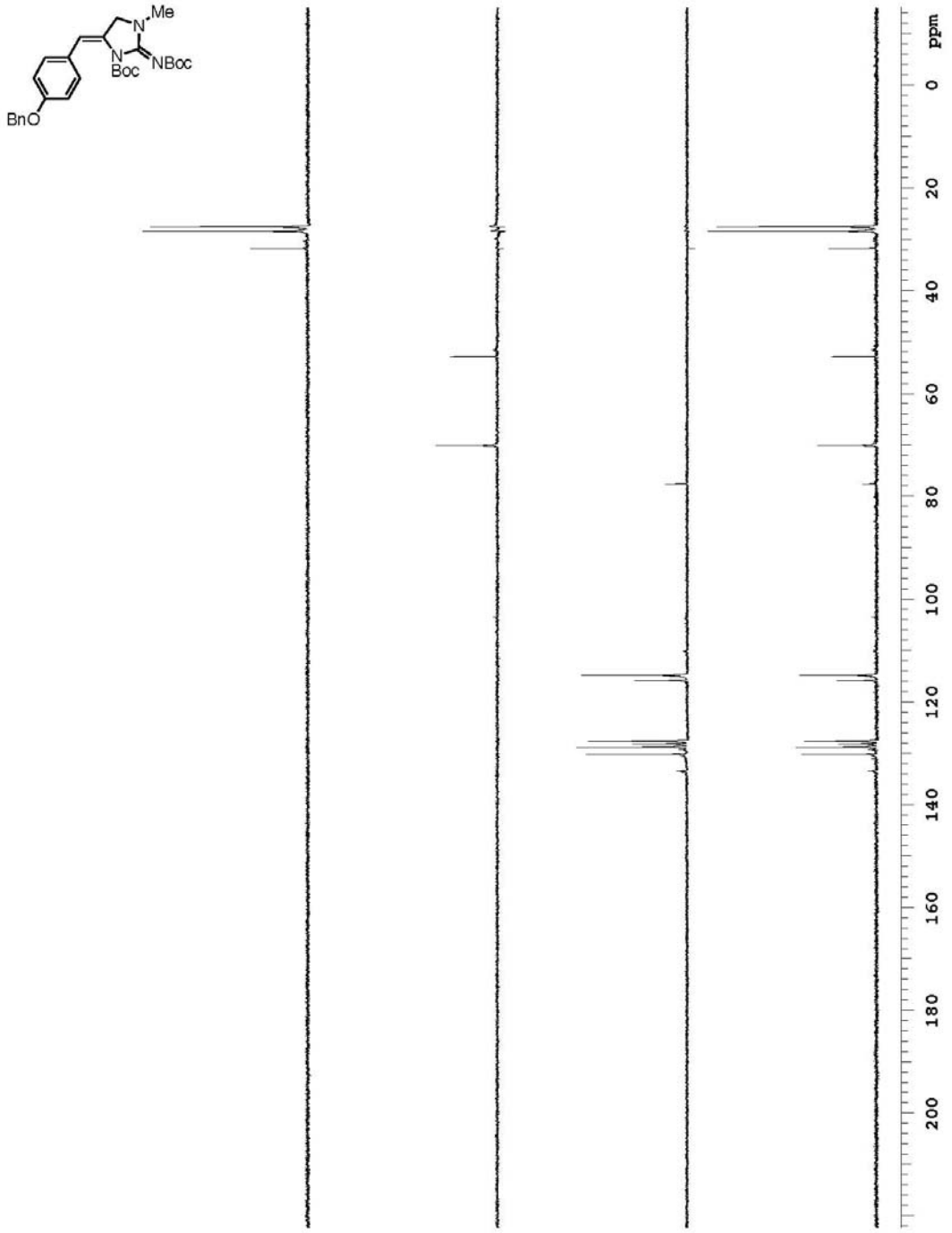
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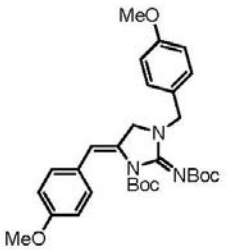
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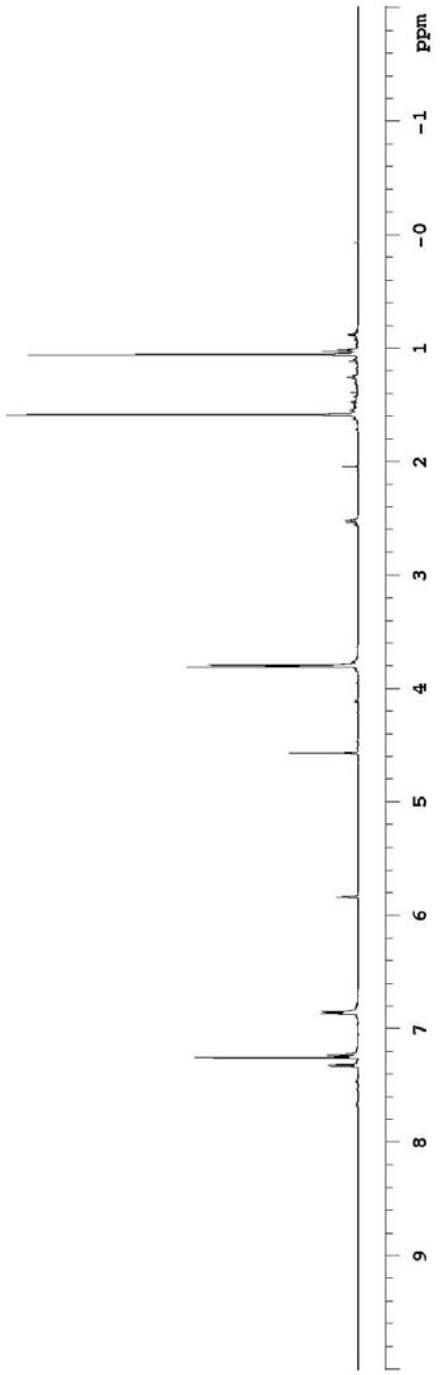
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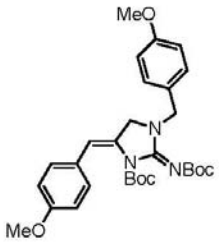
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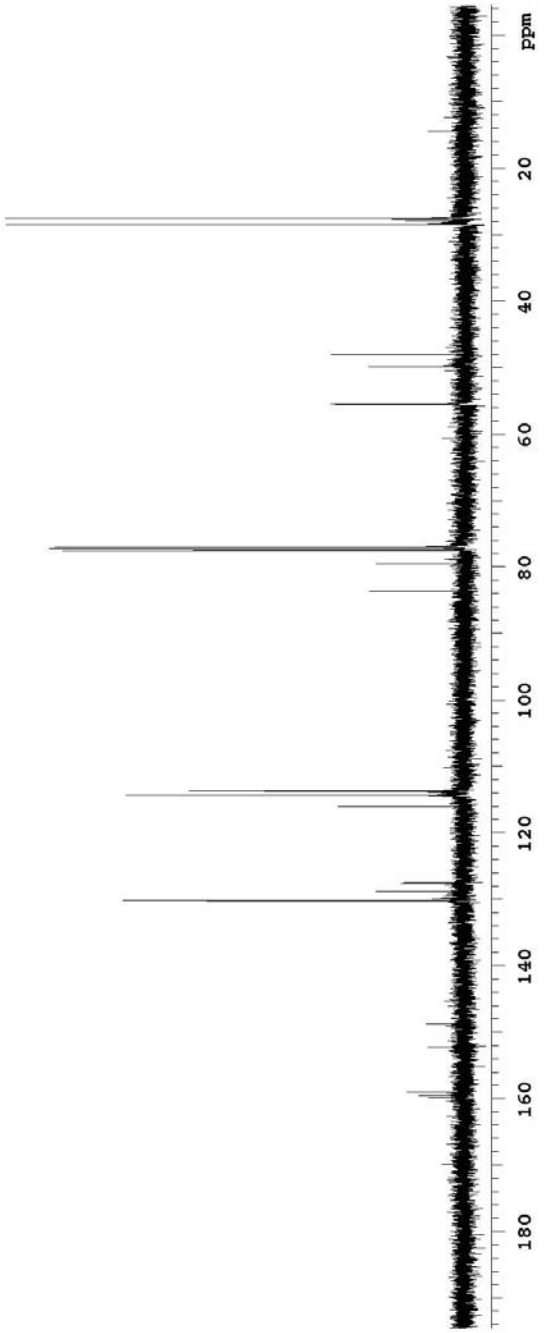
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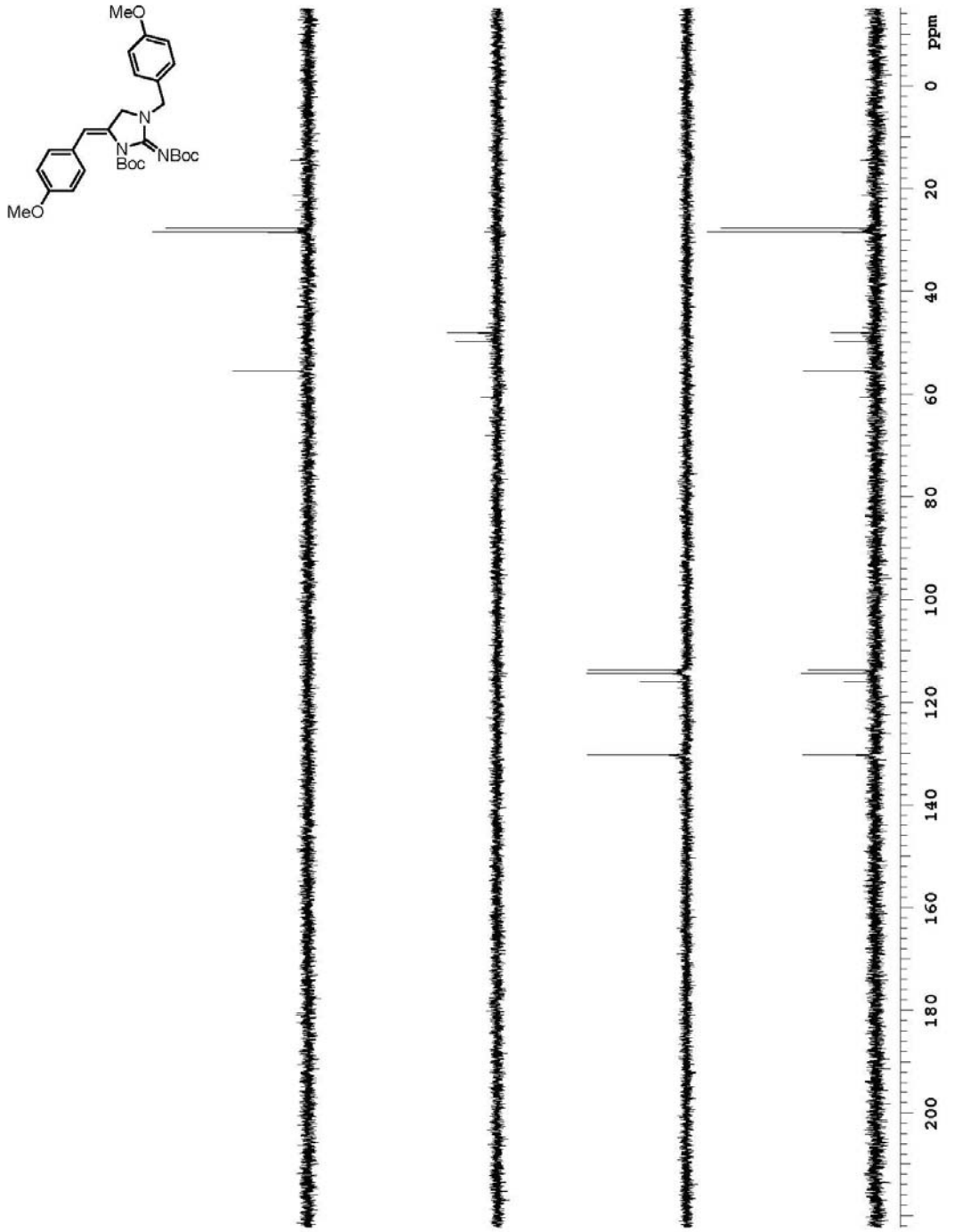
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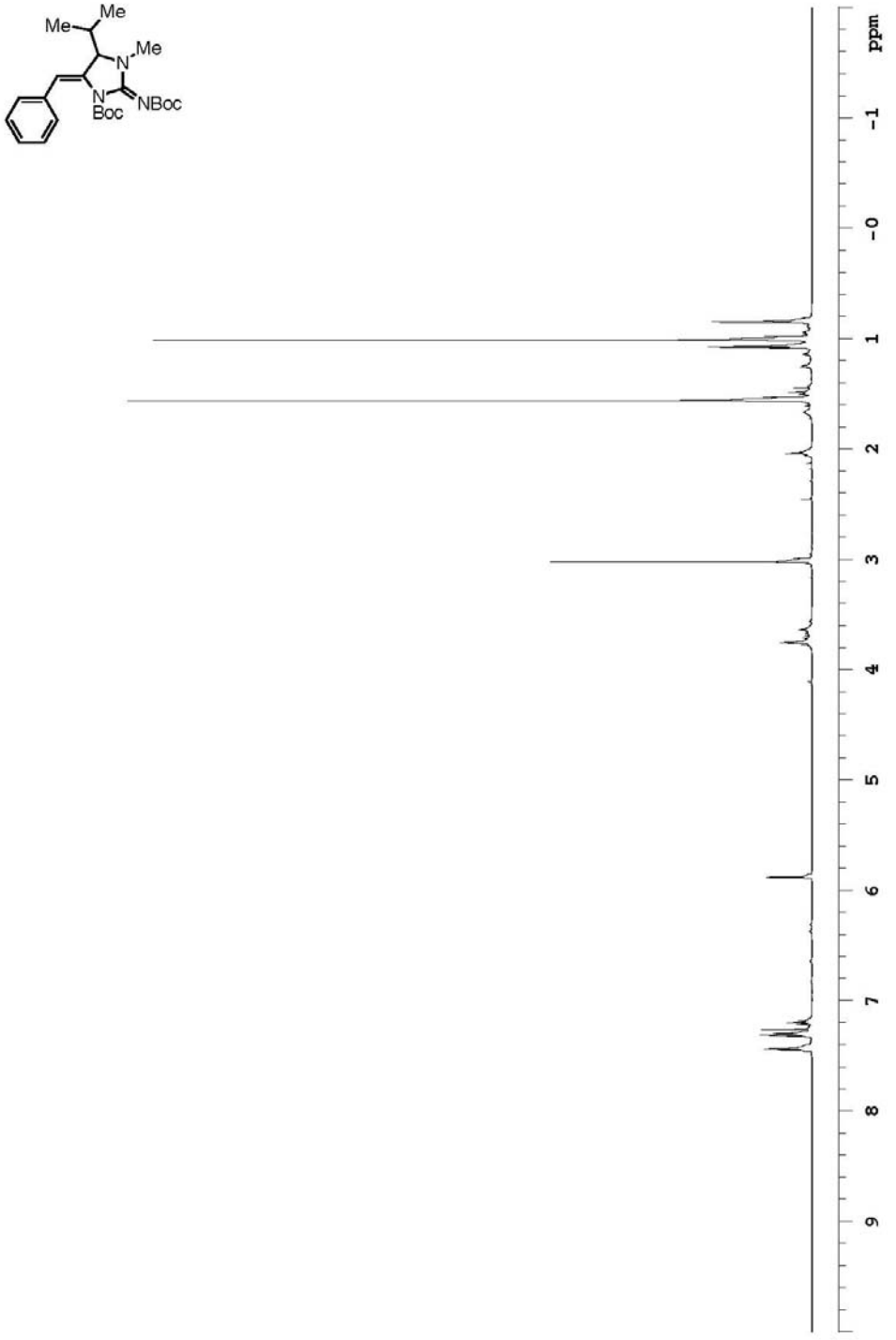
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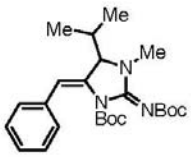
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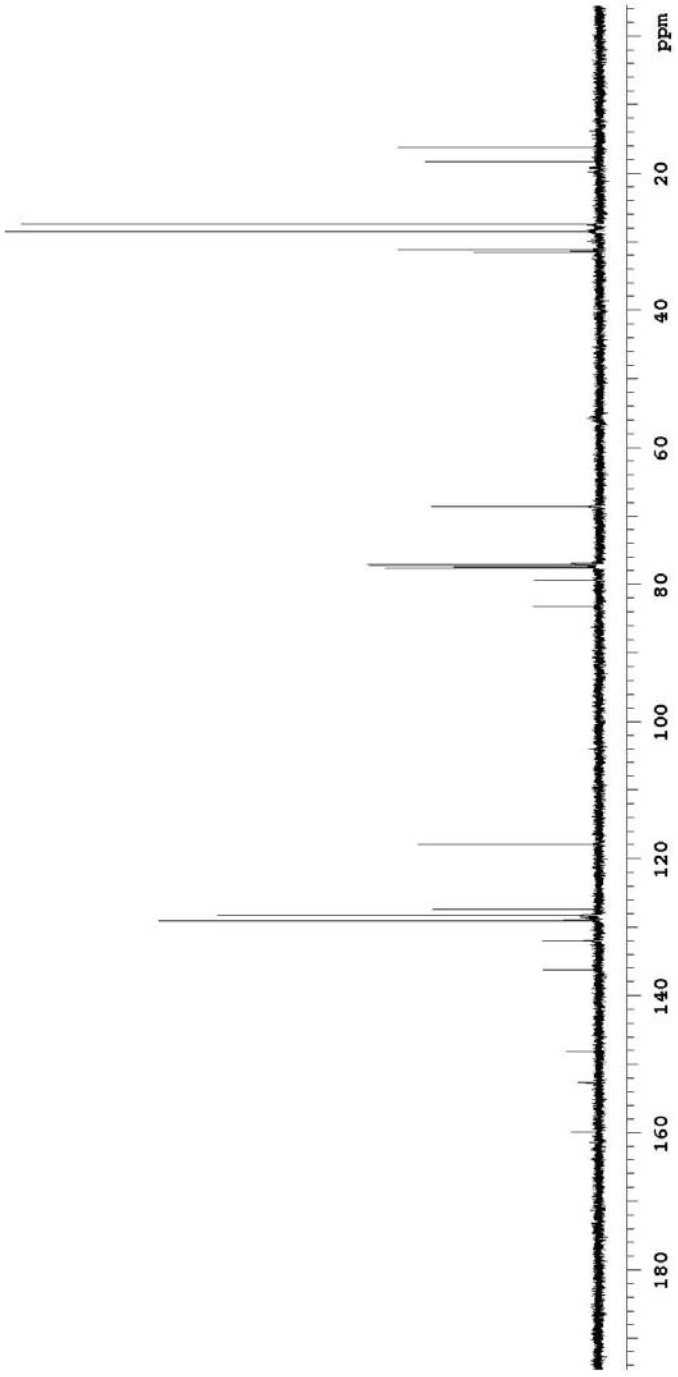
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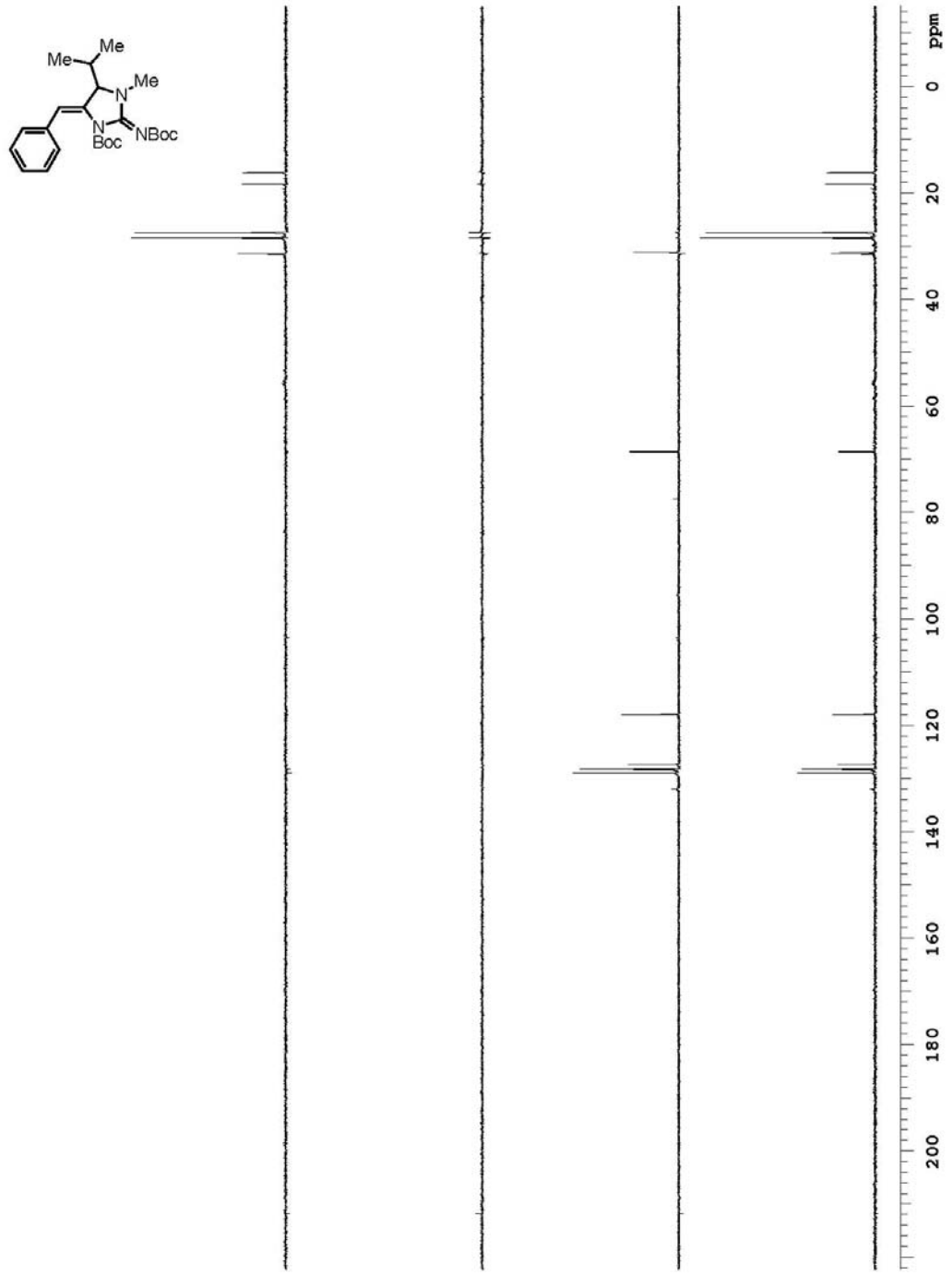
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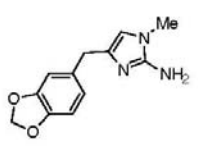
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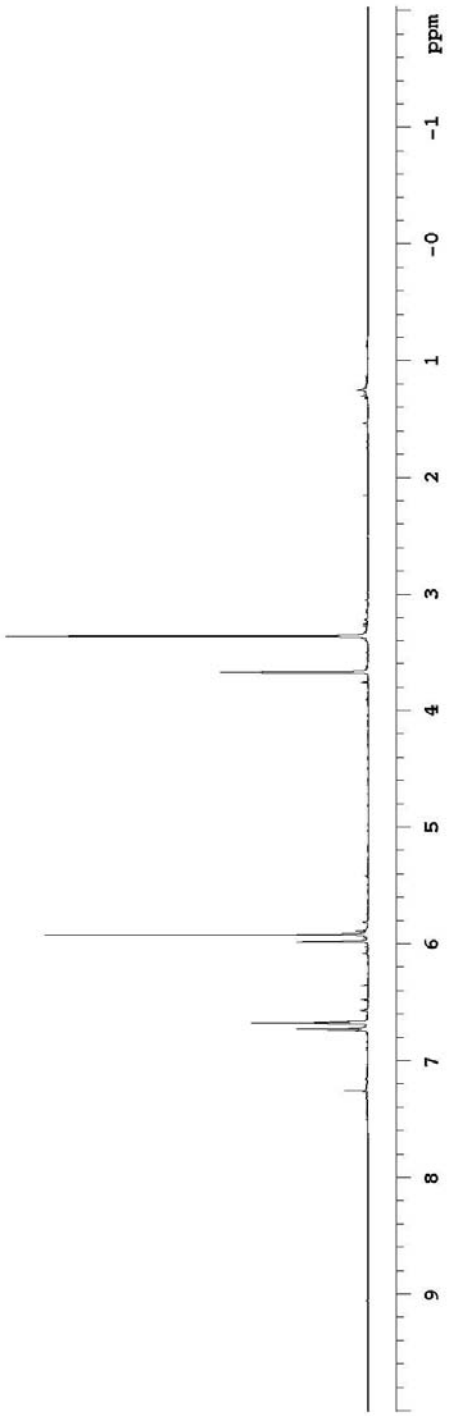
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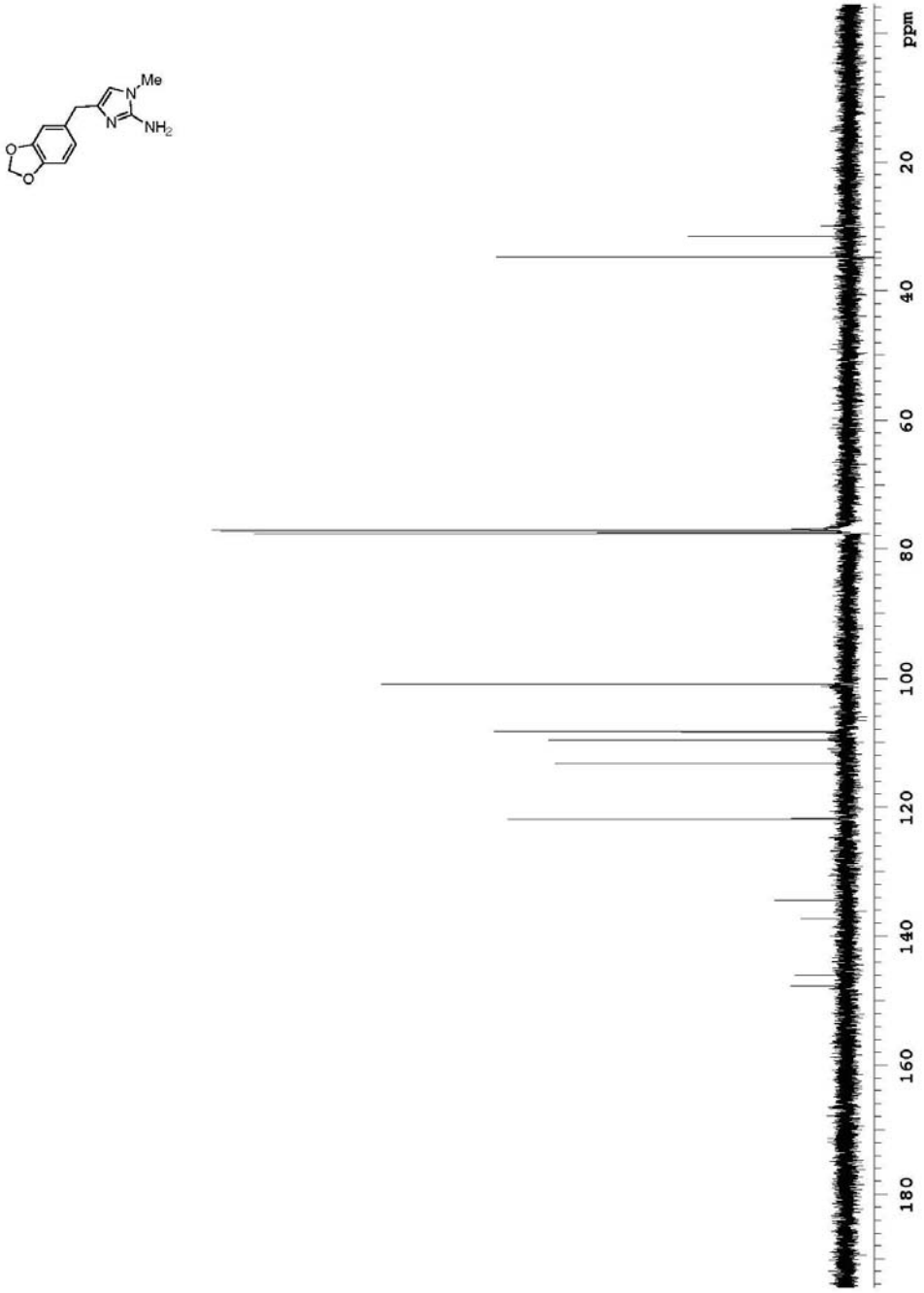
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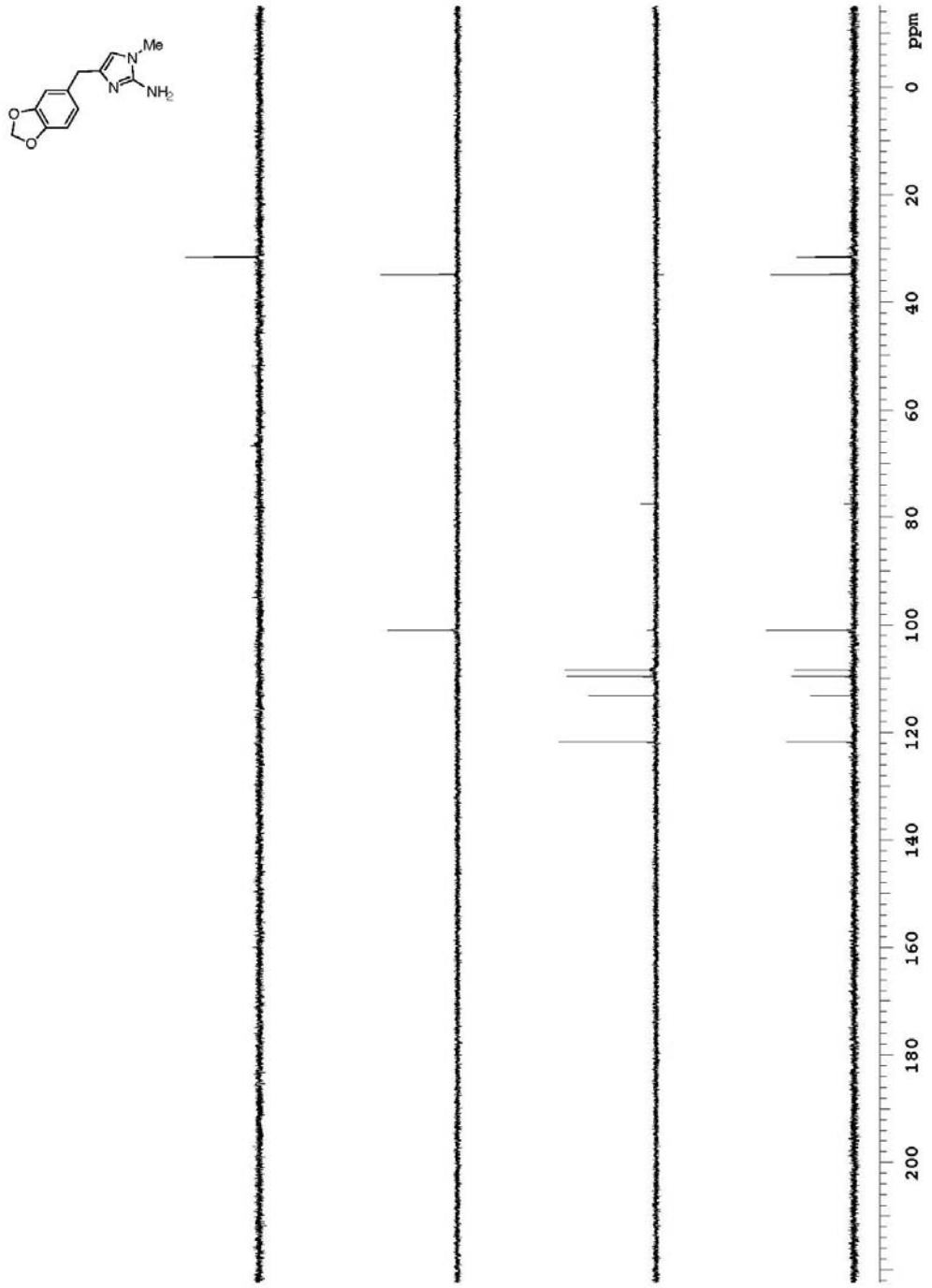
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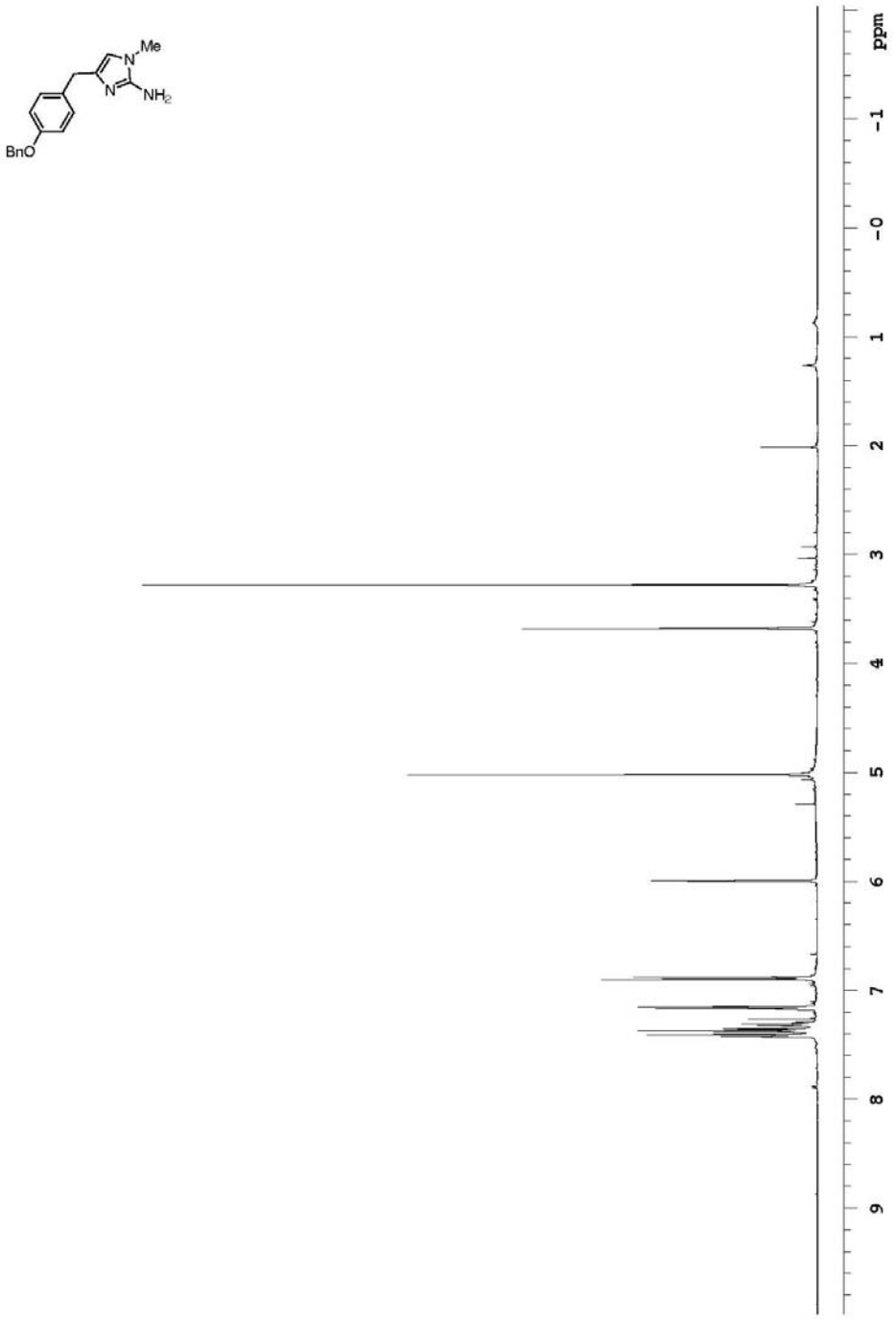
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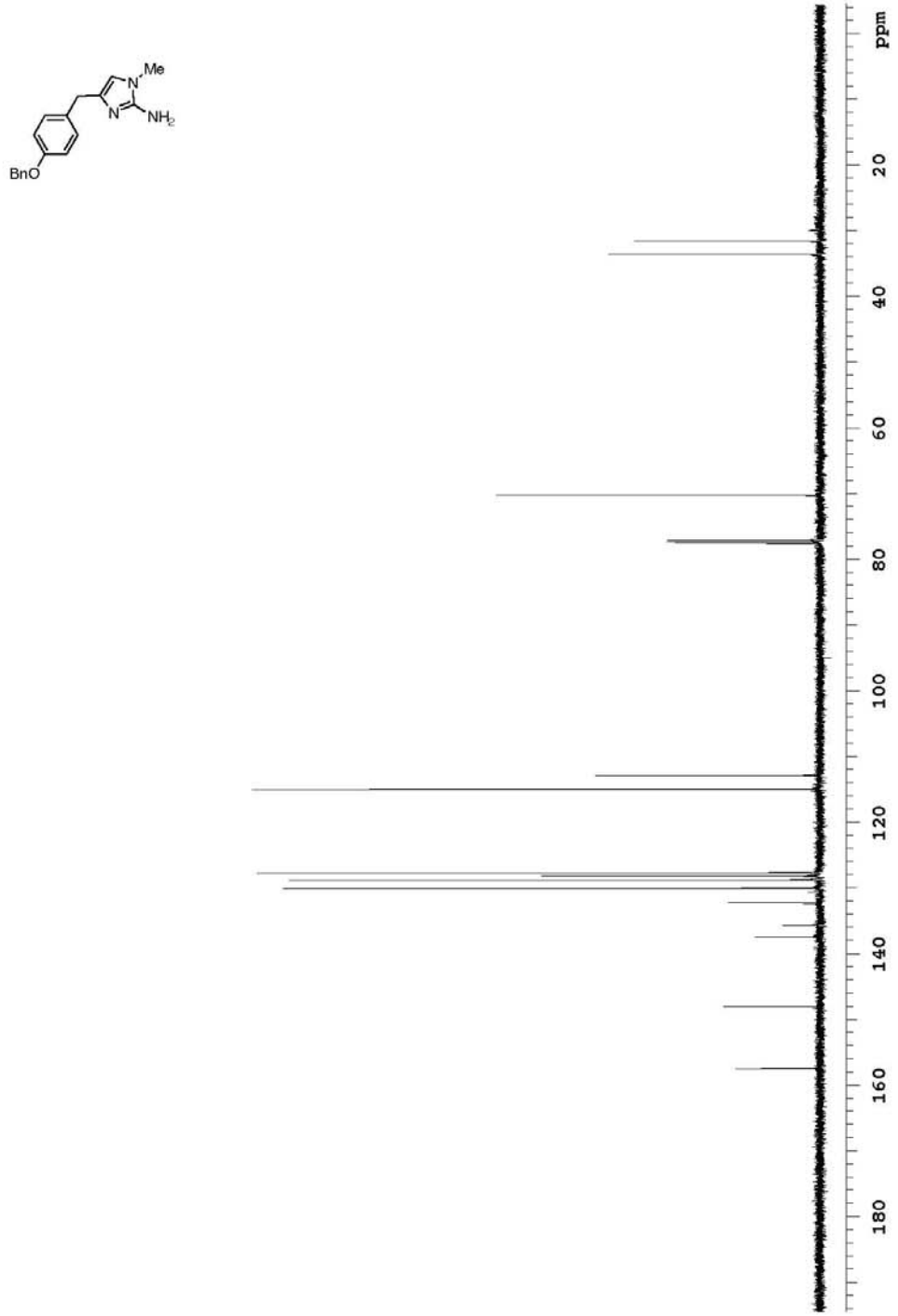
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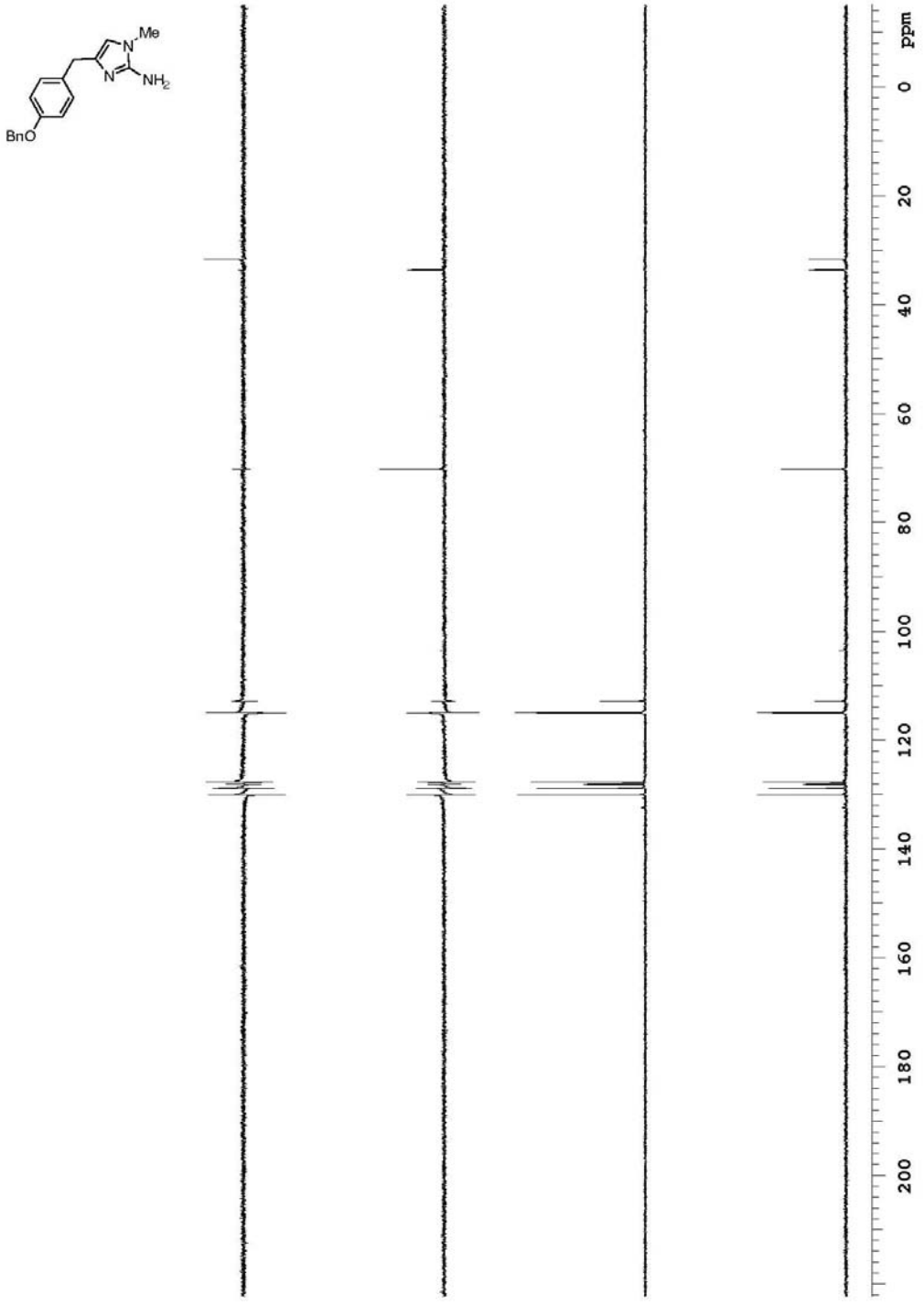
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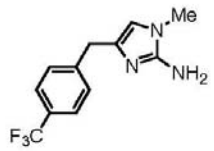
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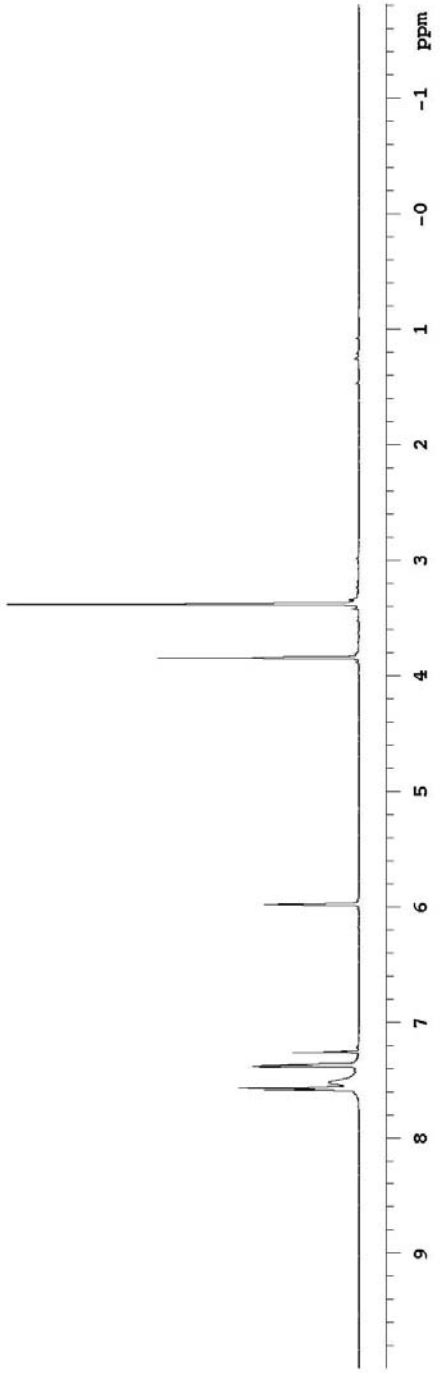
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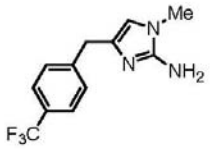
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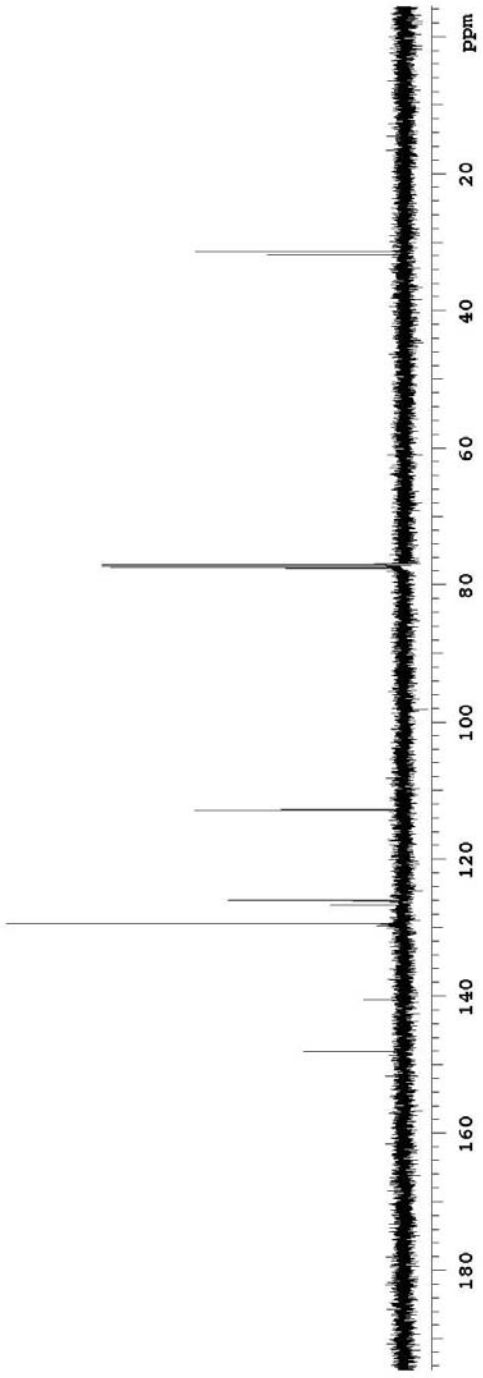
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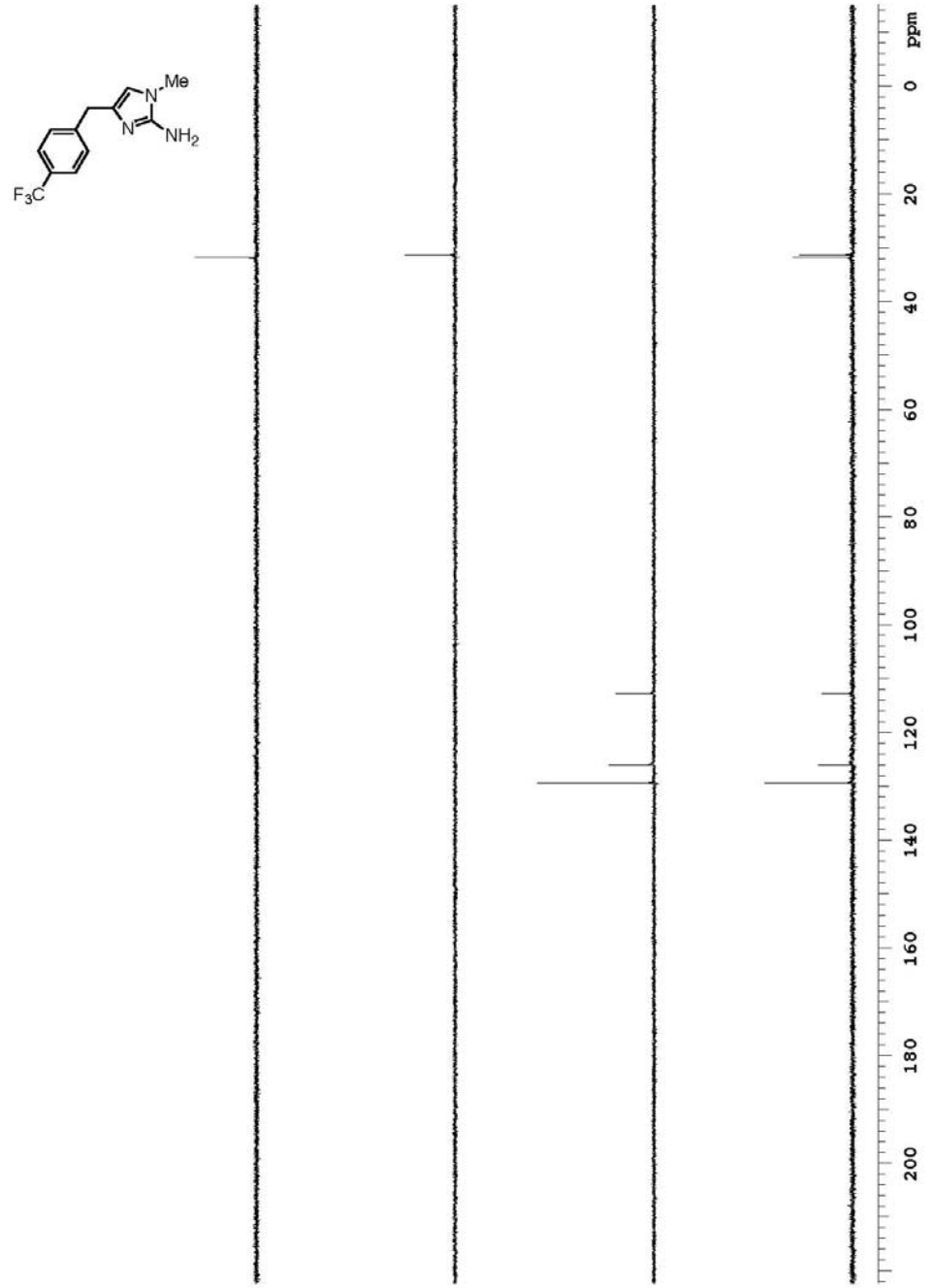
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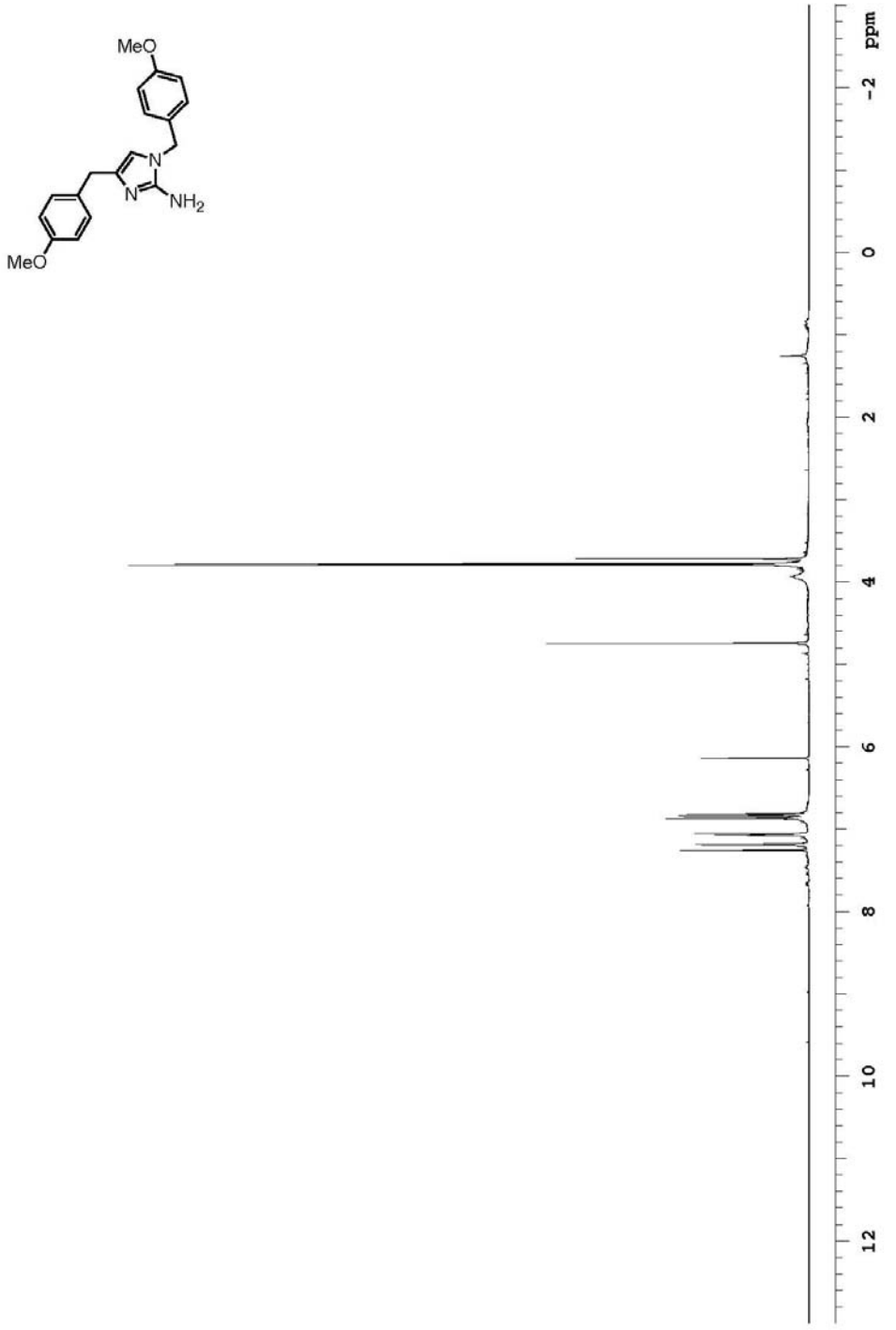
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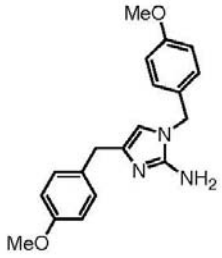
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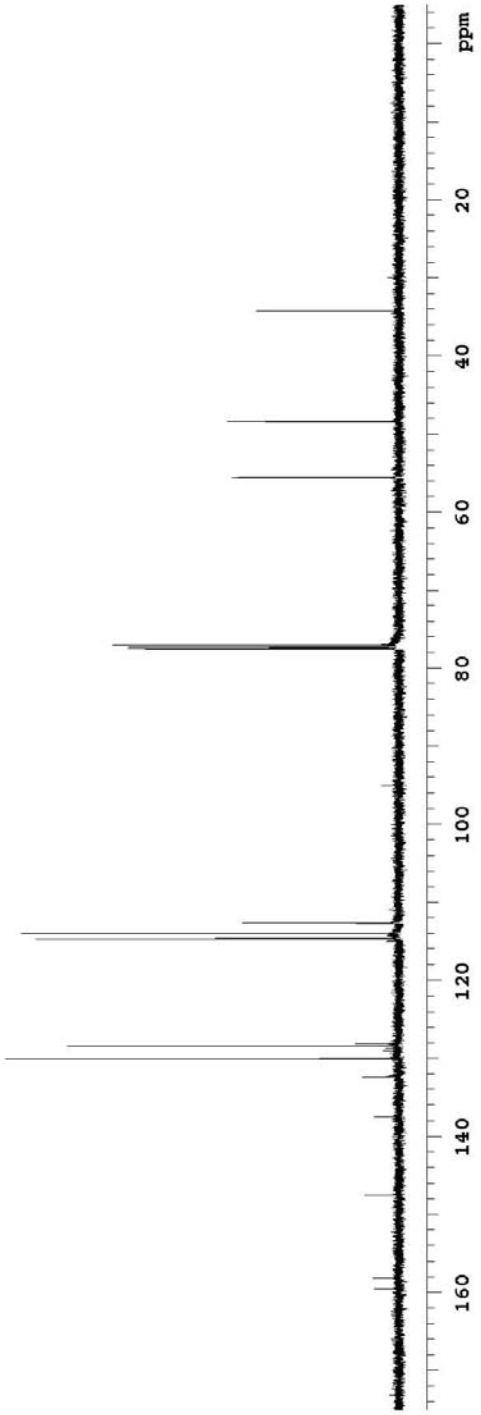
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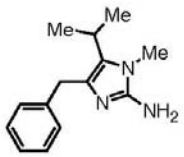
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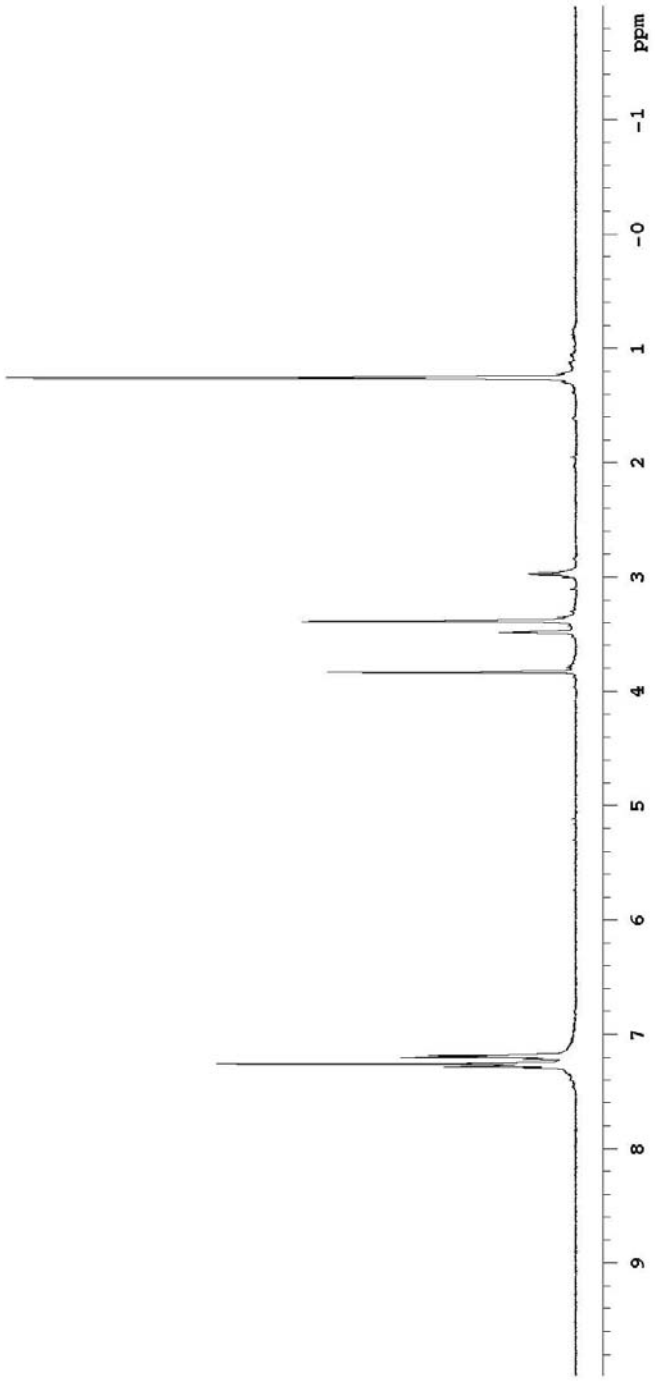
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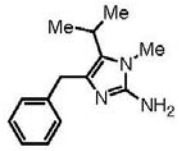
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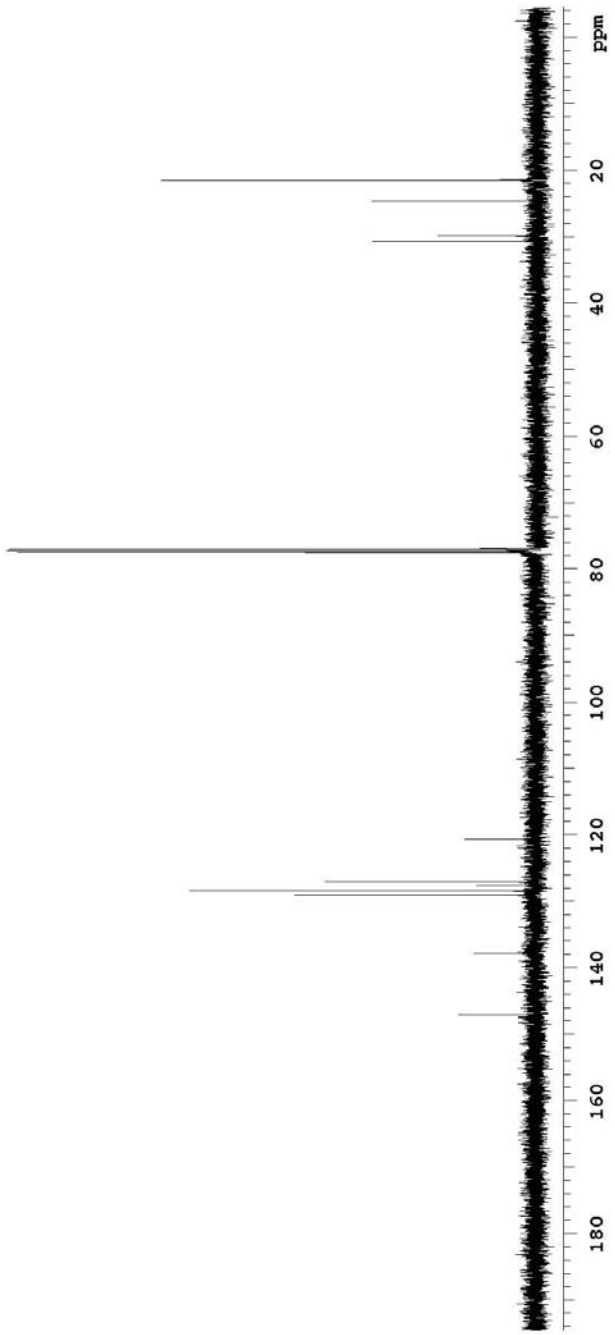
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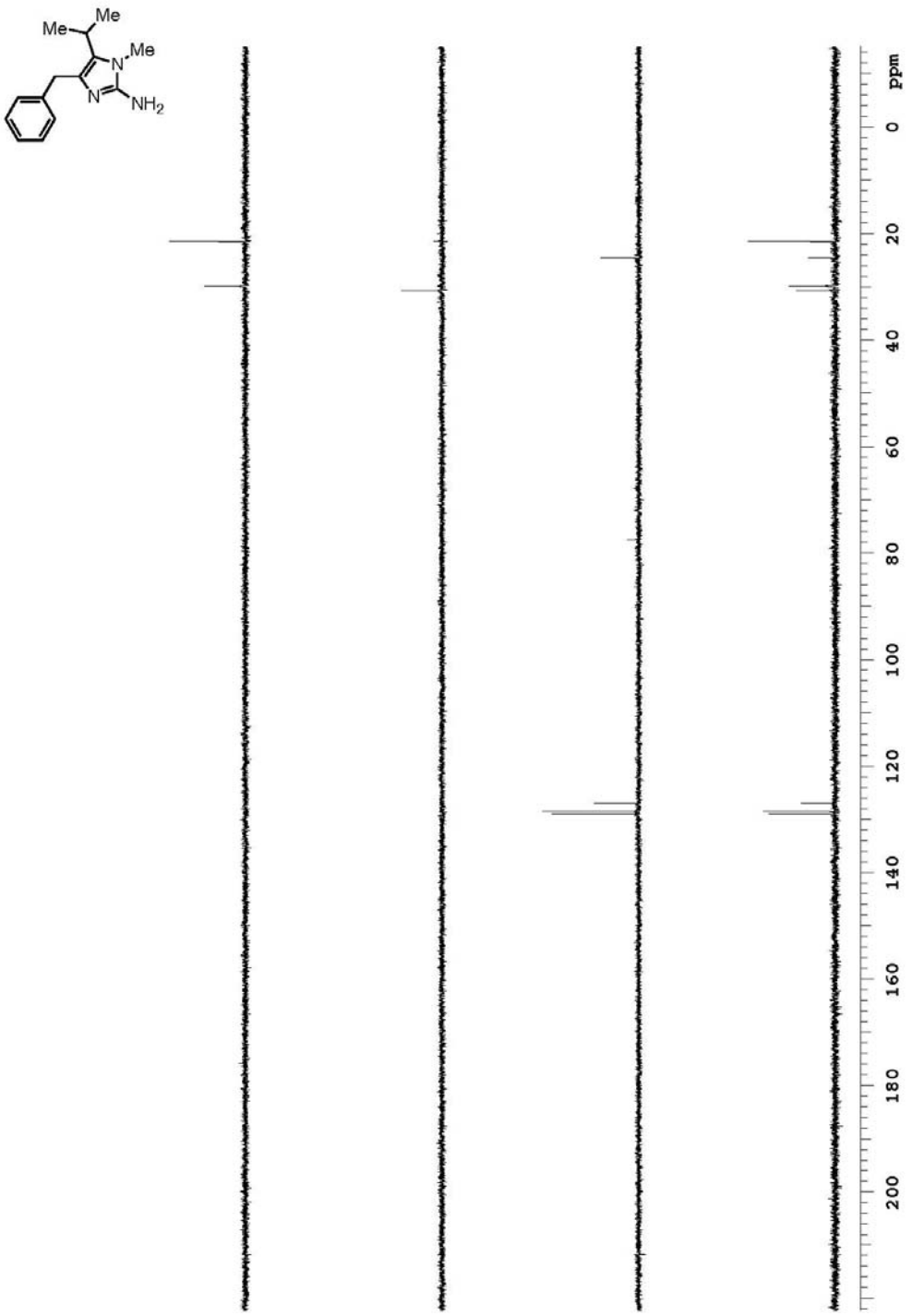
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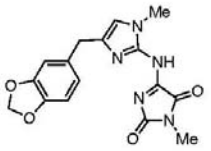
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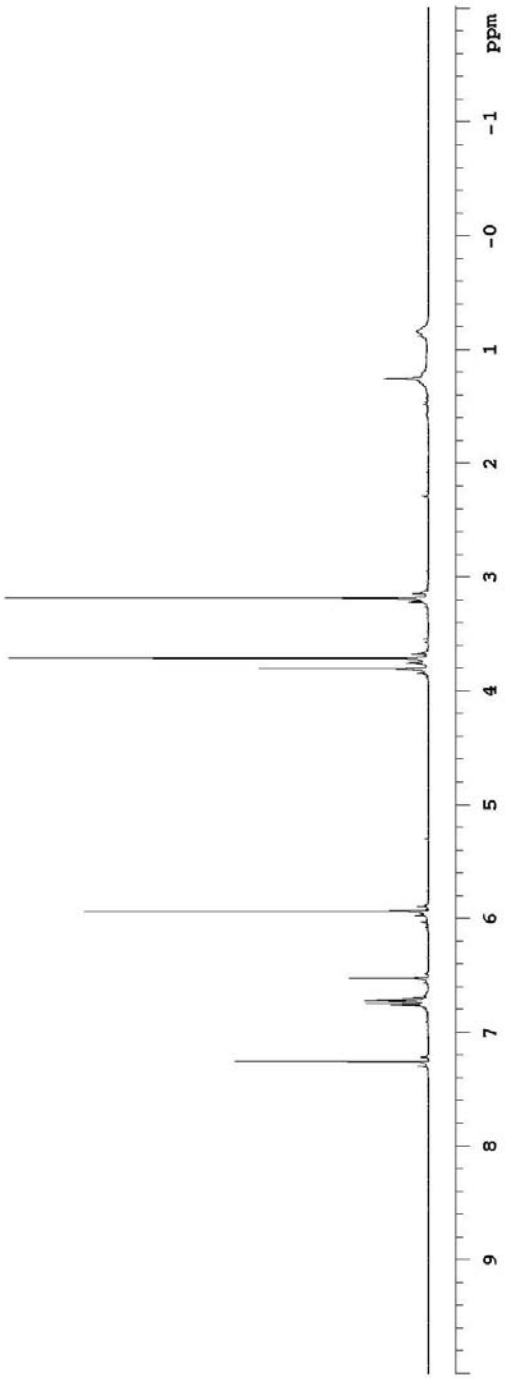
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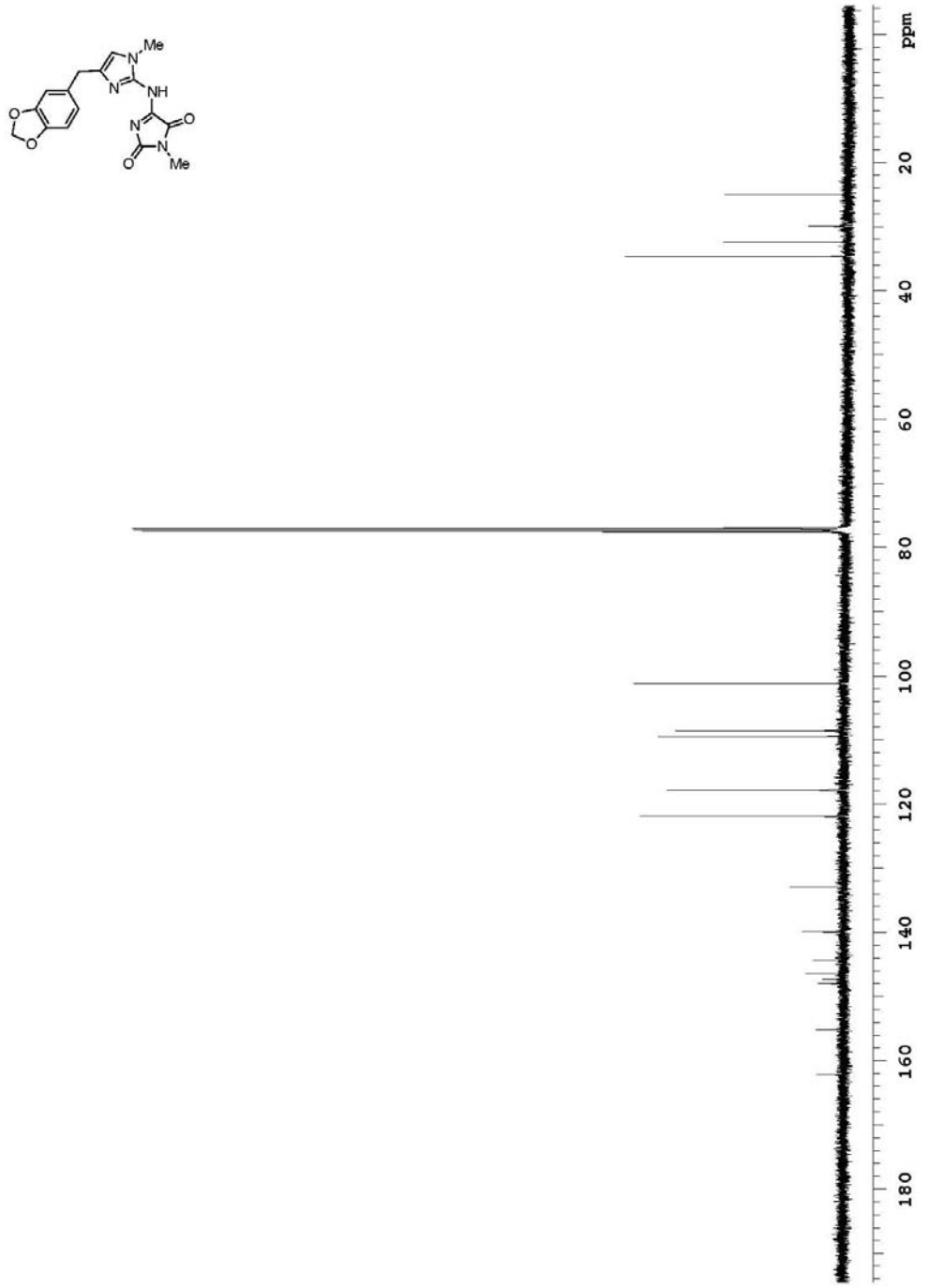
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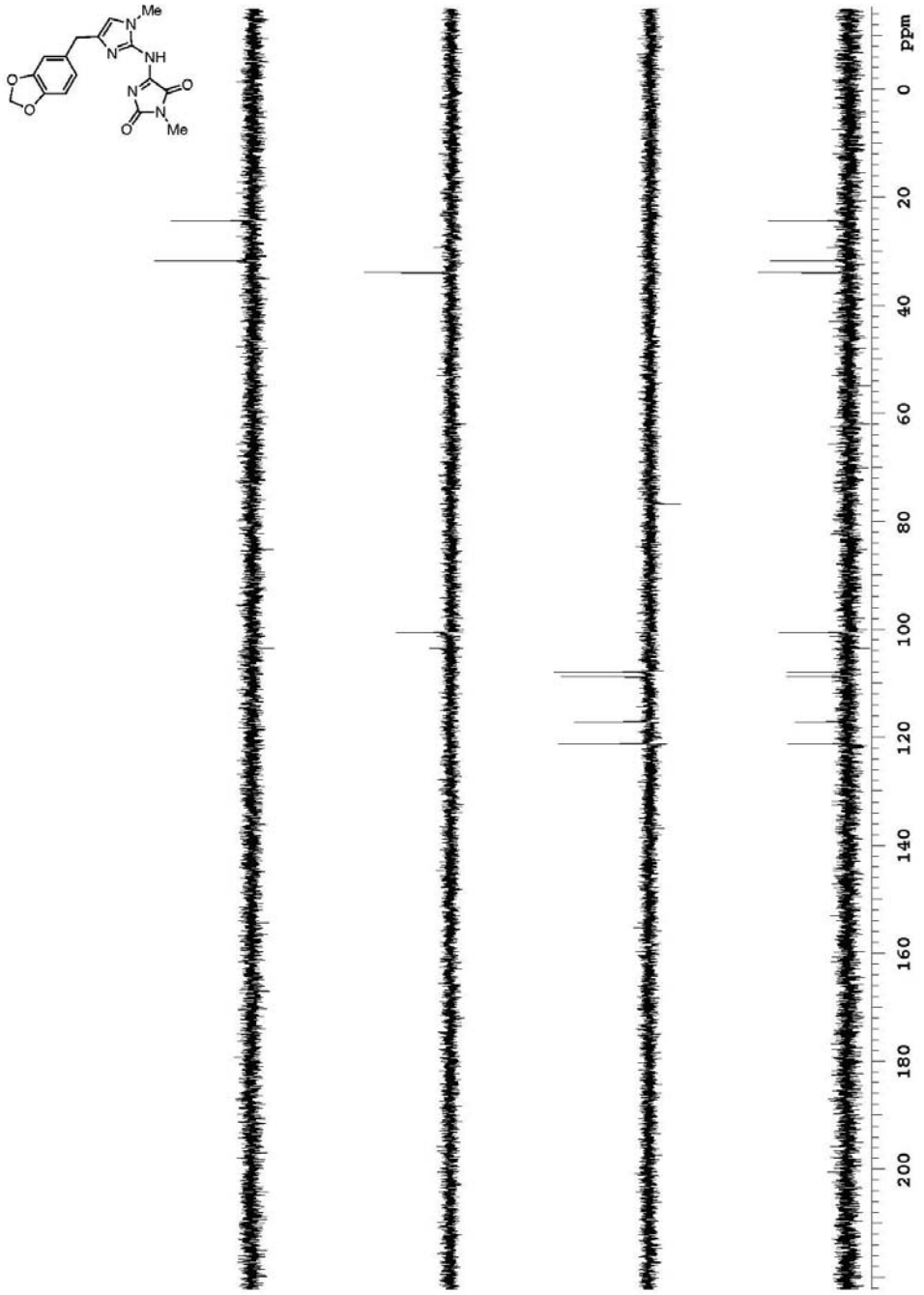
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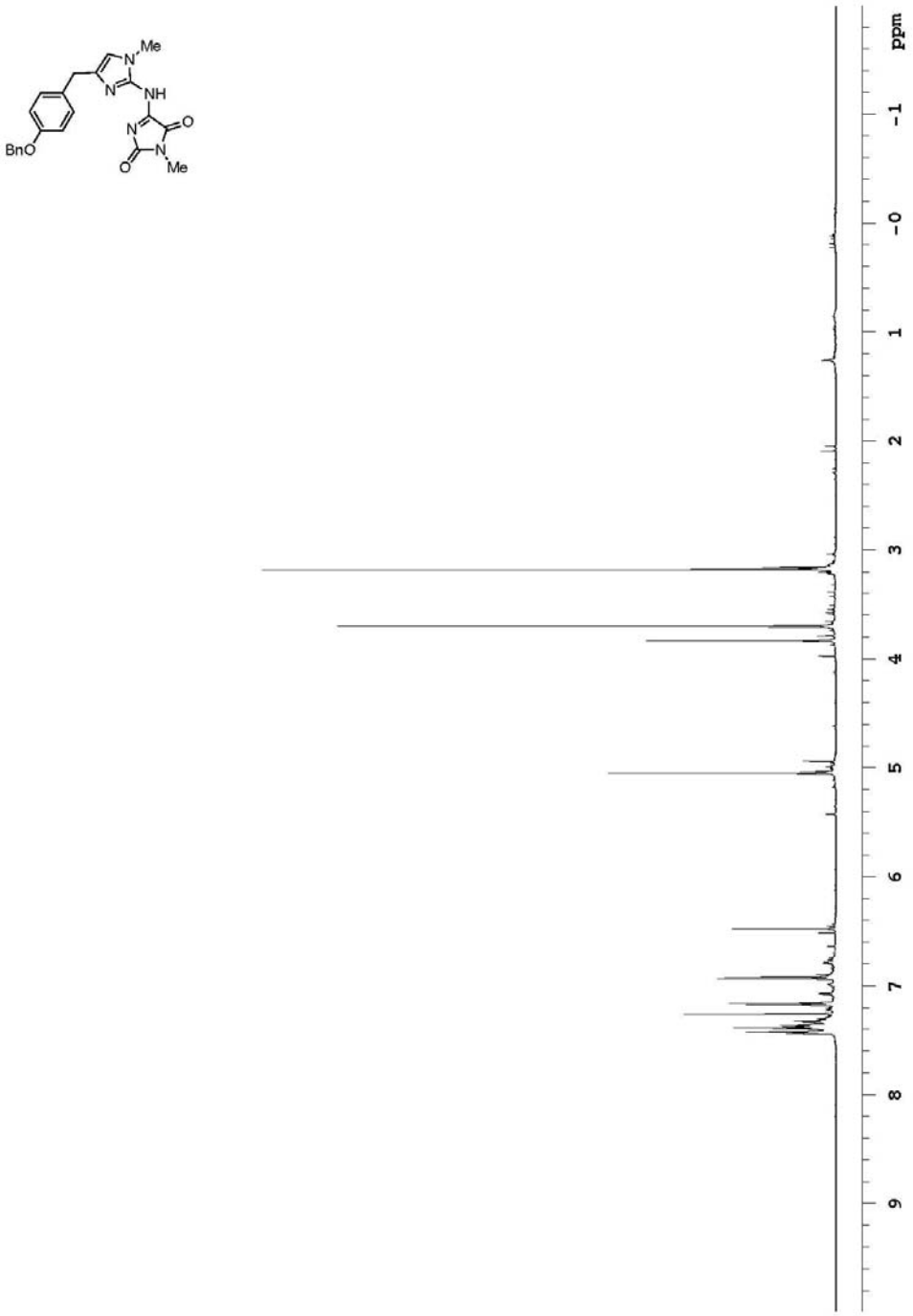
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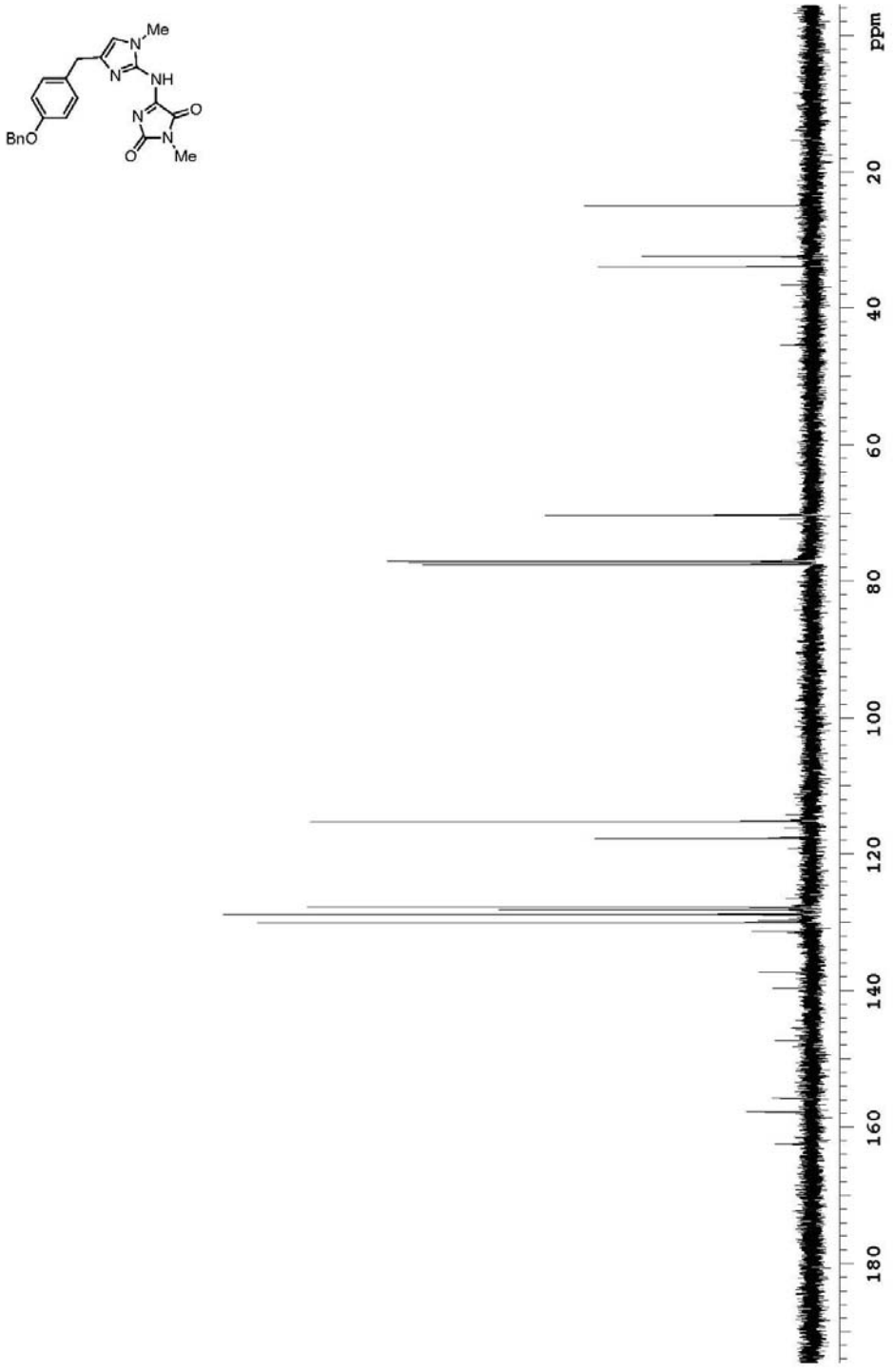
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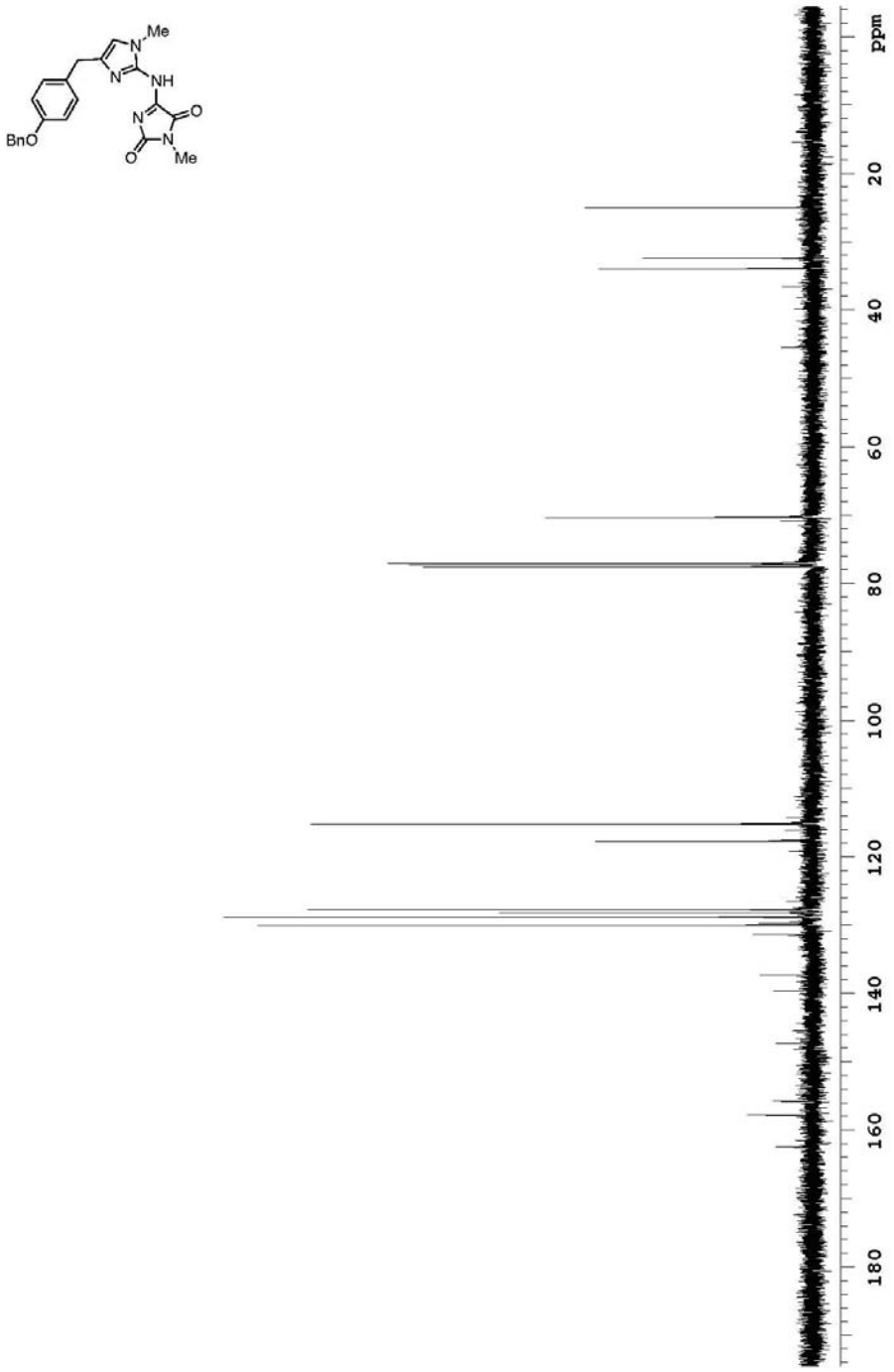
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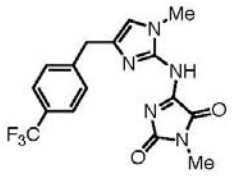
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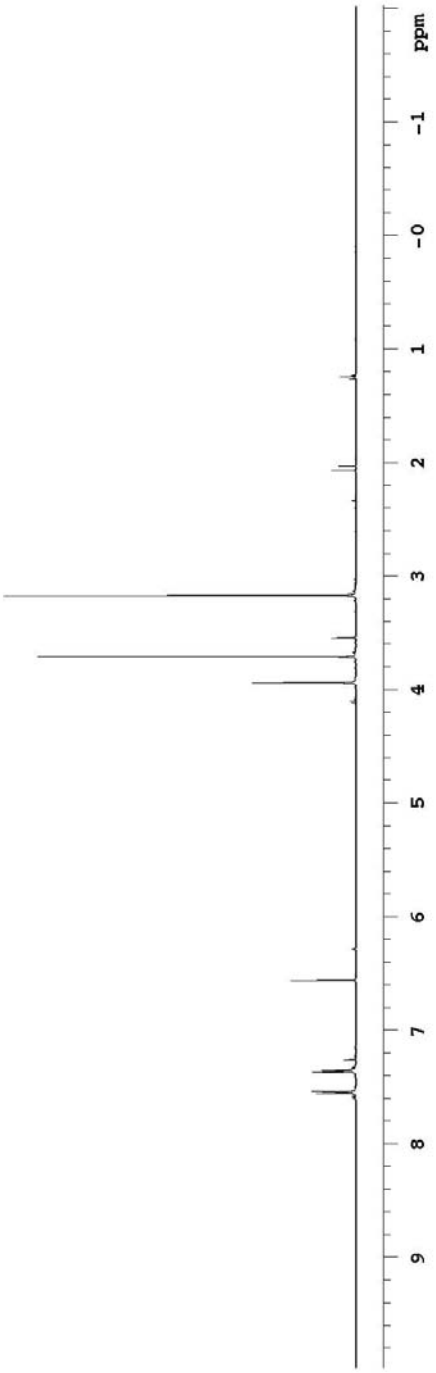
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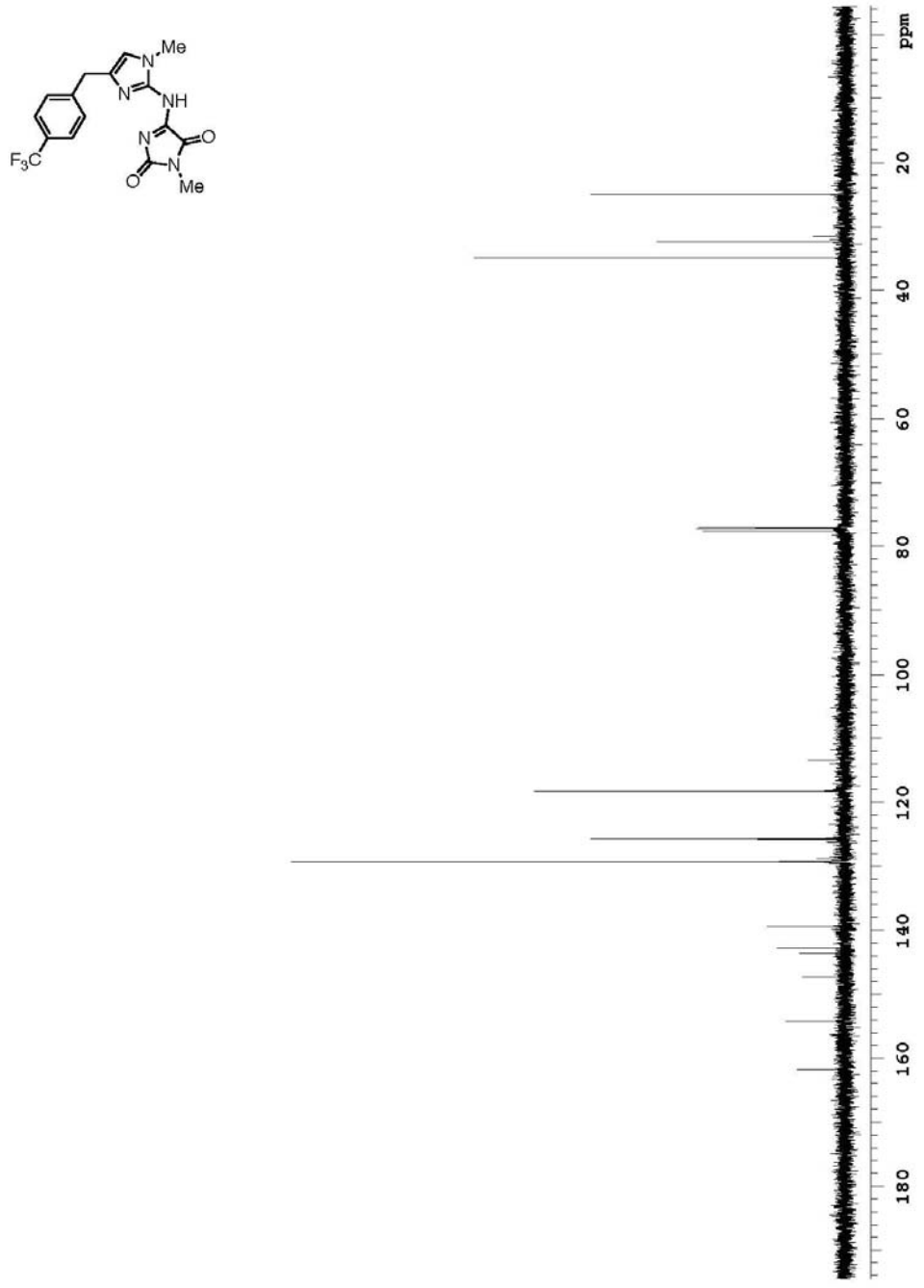
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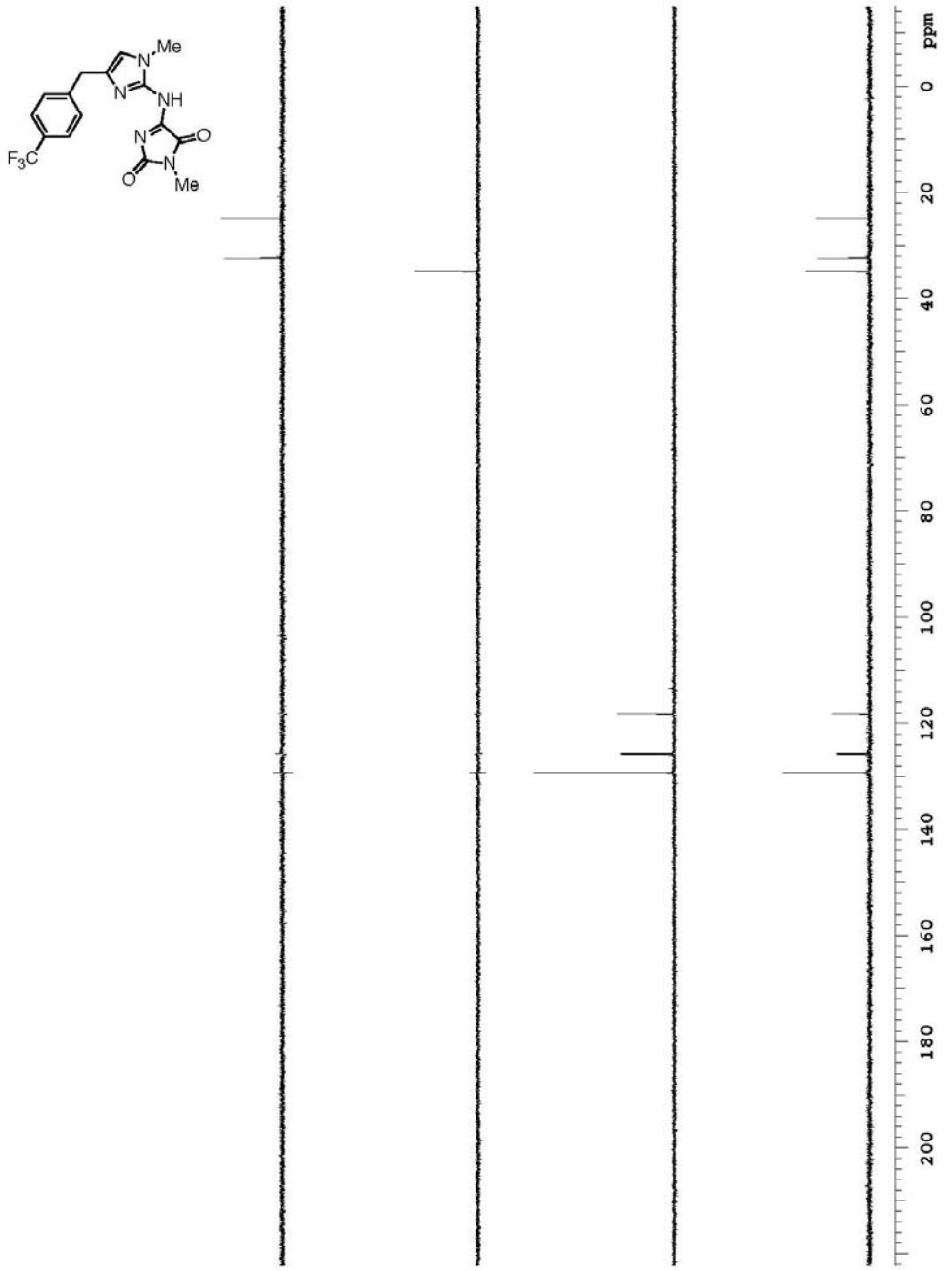
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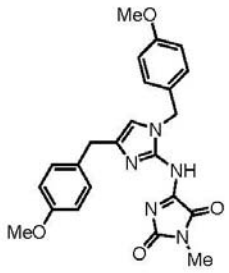
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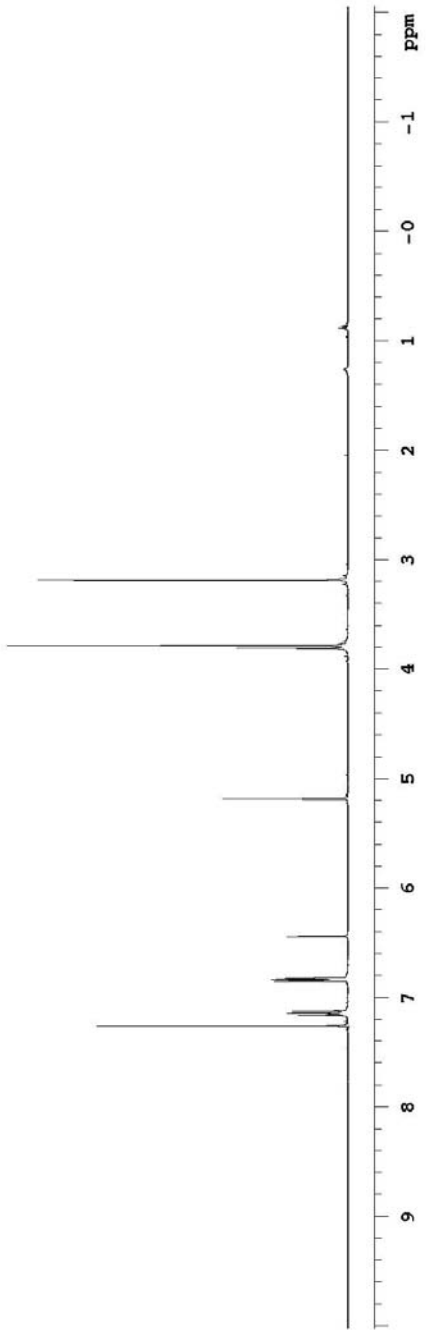
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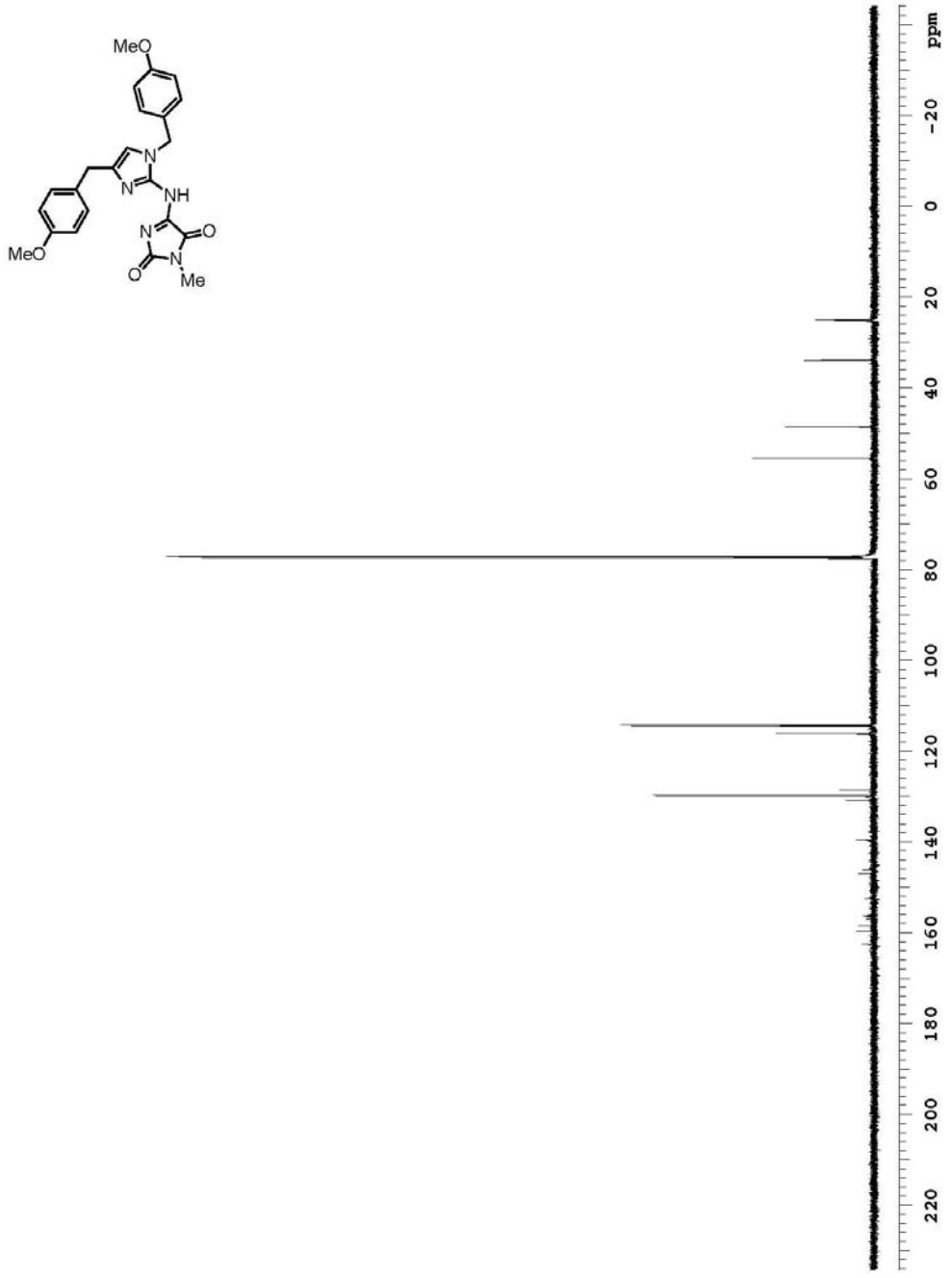
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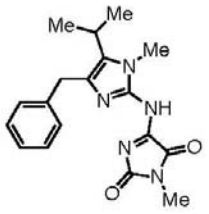
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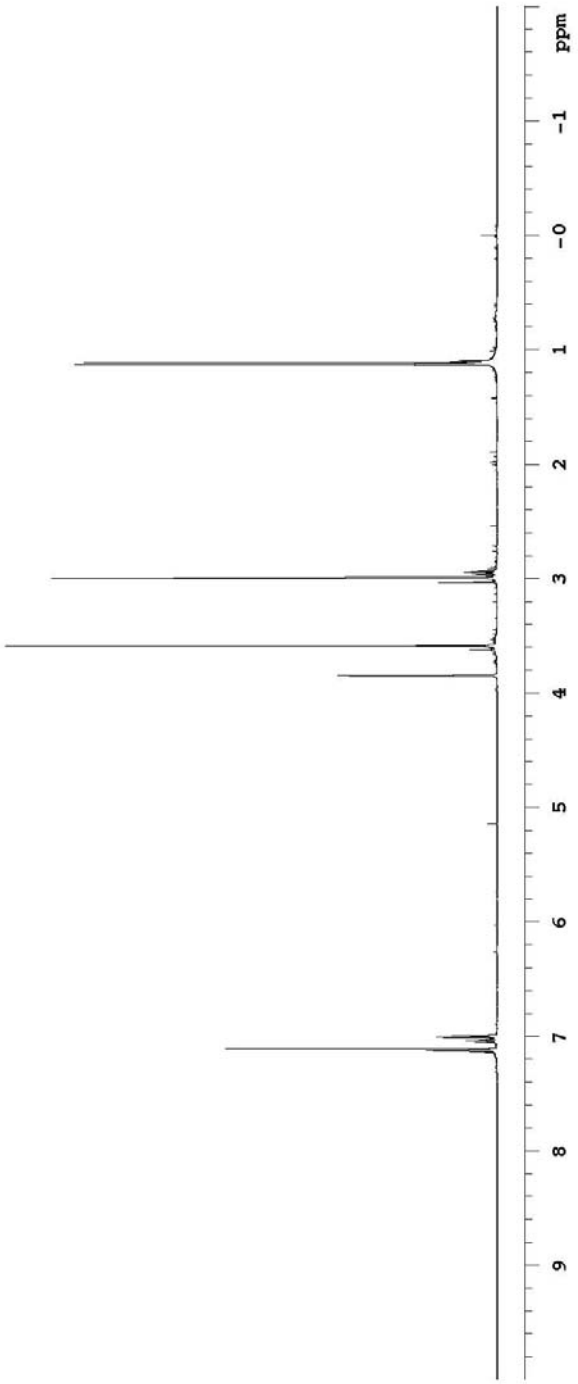
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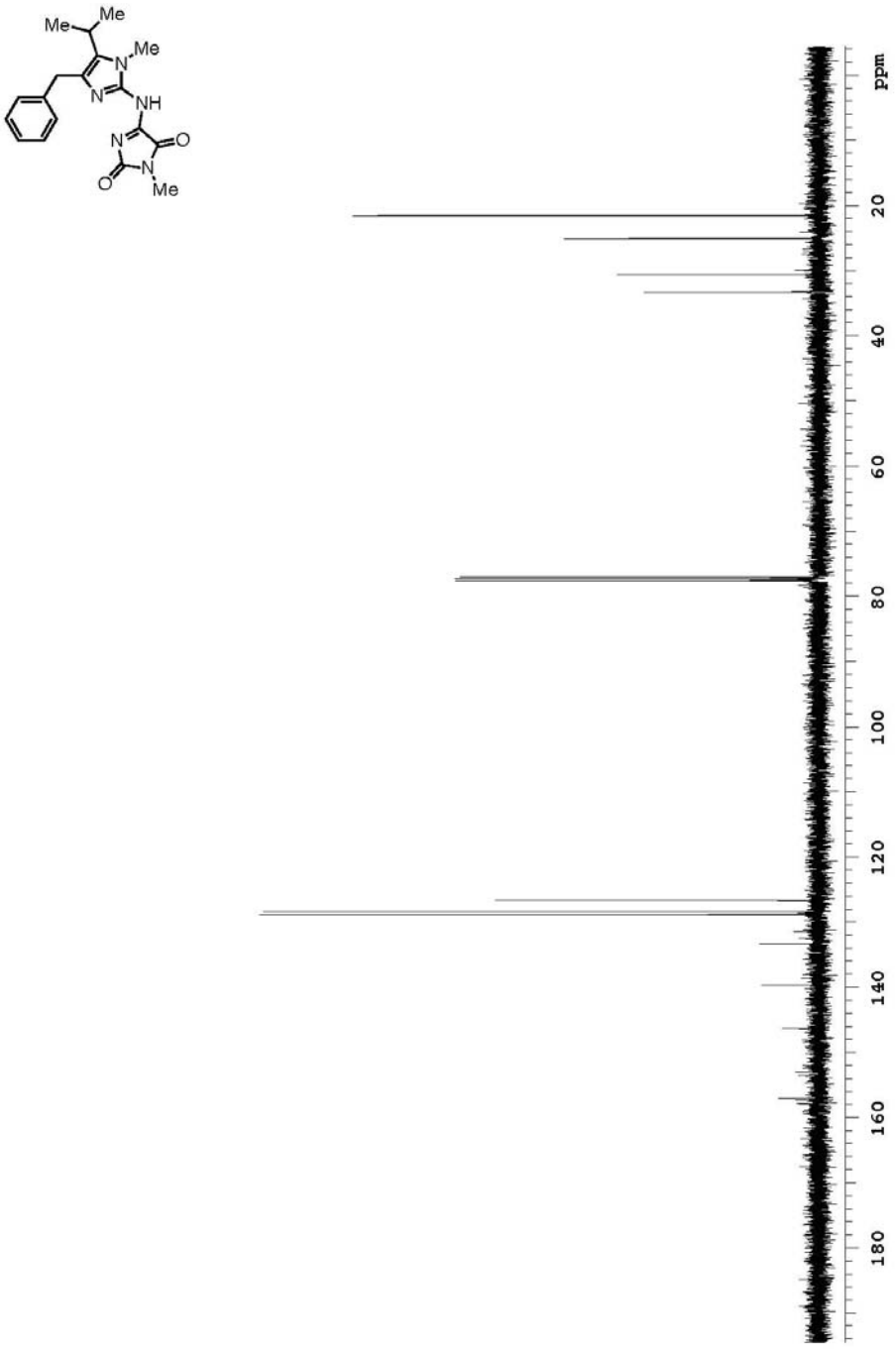
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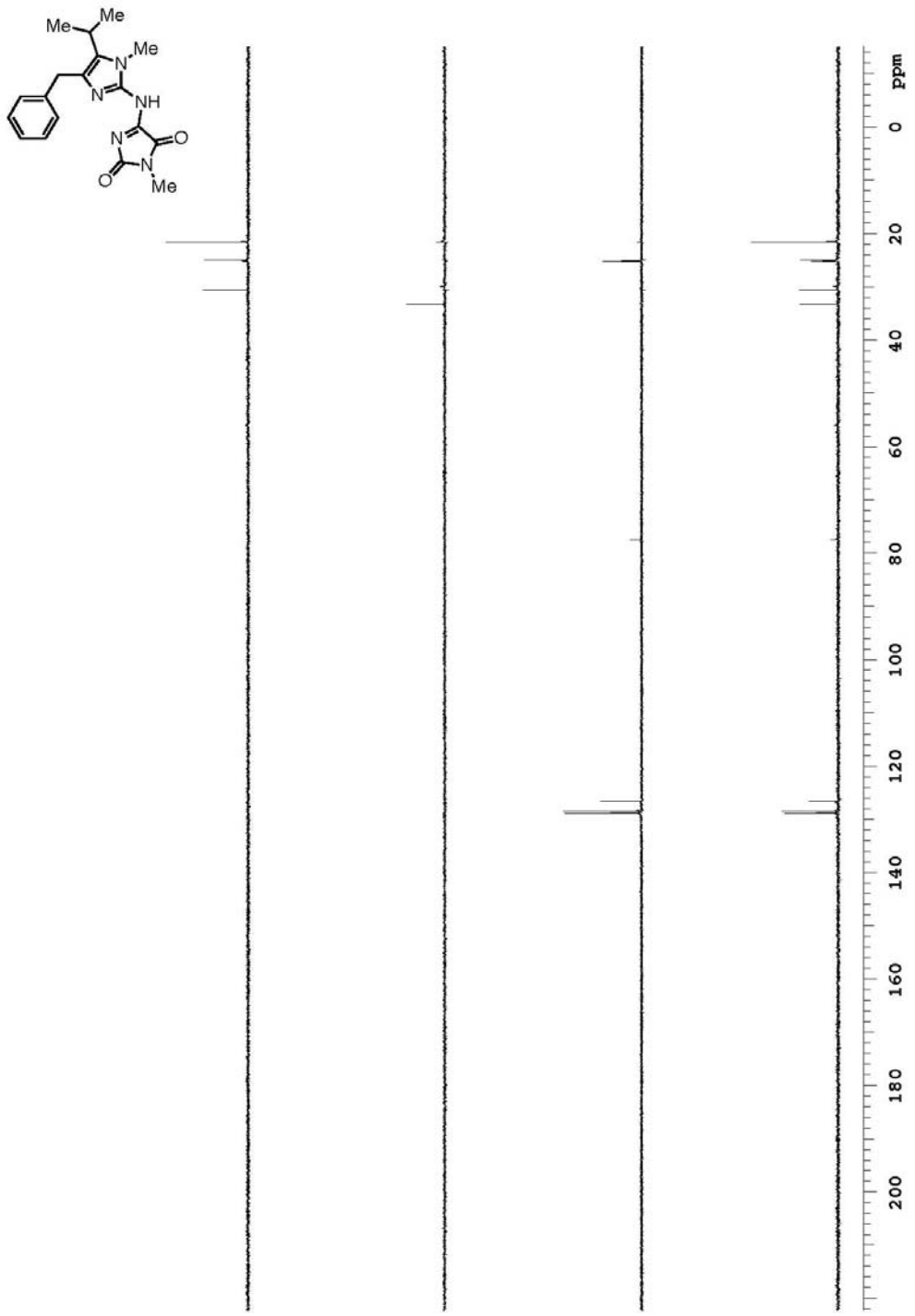
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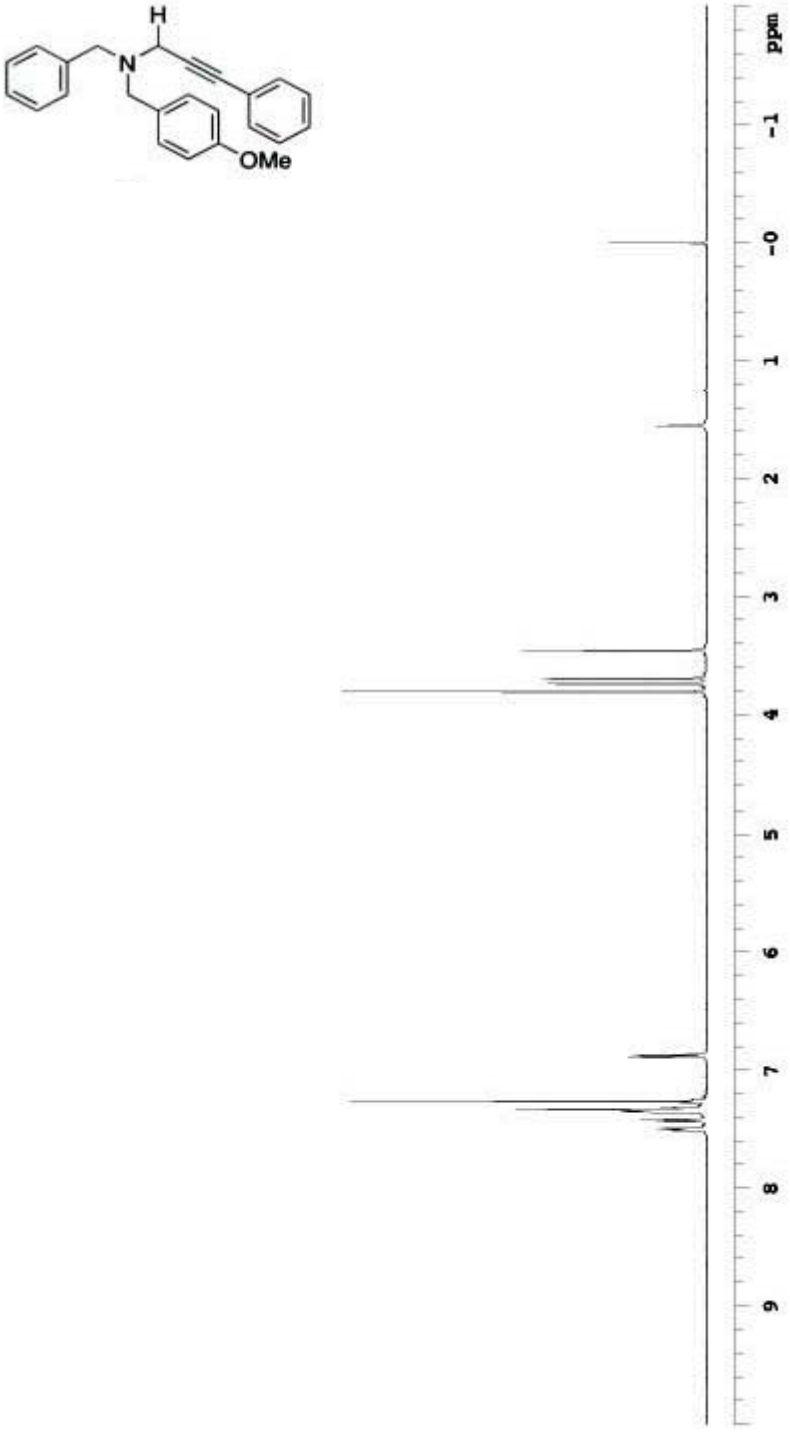
APPENDIX B

^{1}H, ^{13}C AND ^{13}C DEPT SPECTRA CHAPTER 3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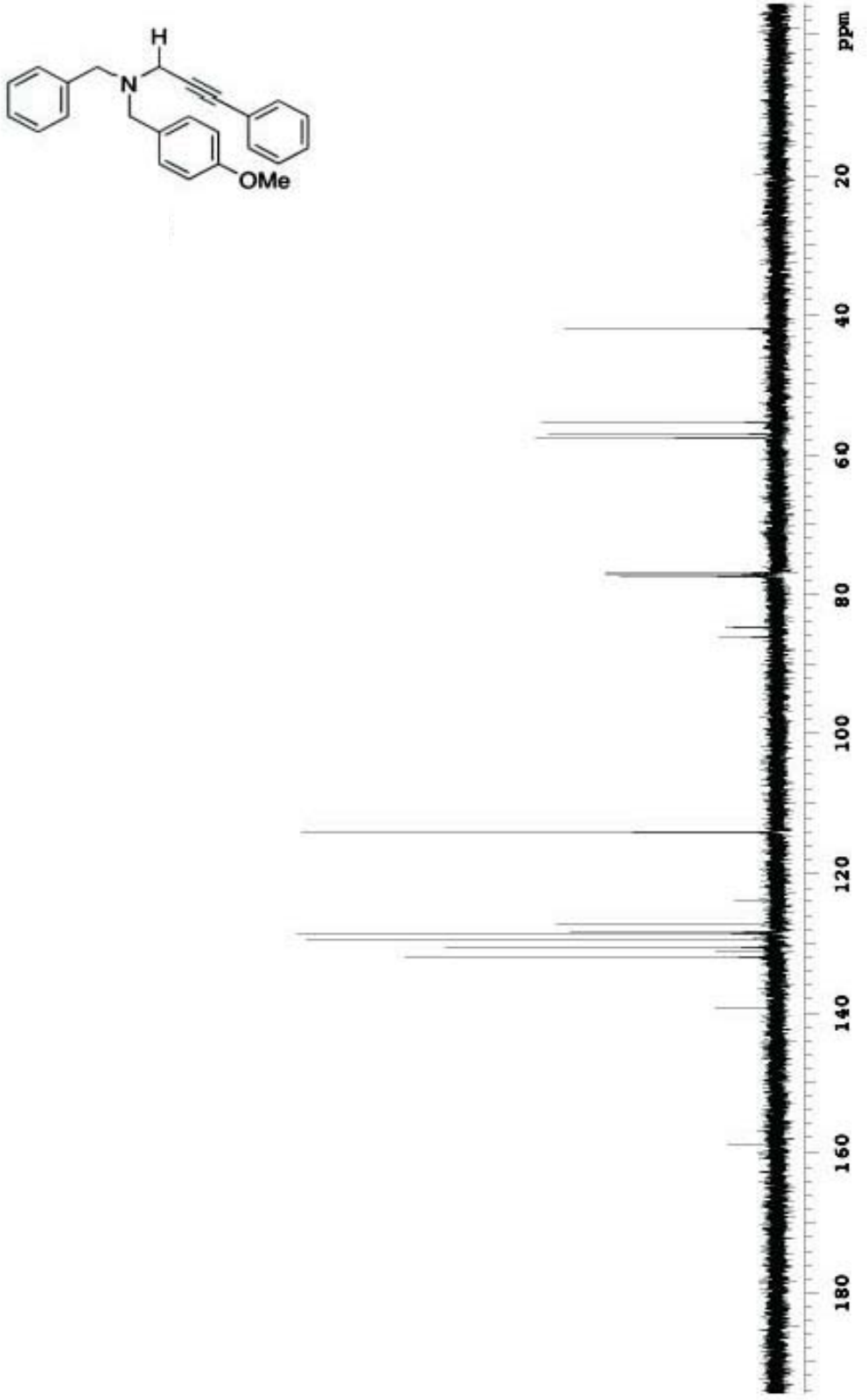
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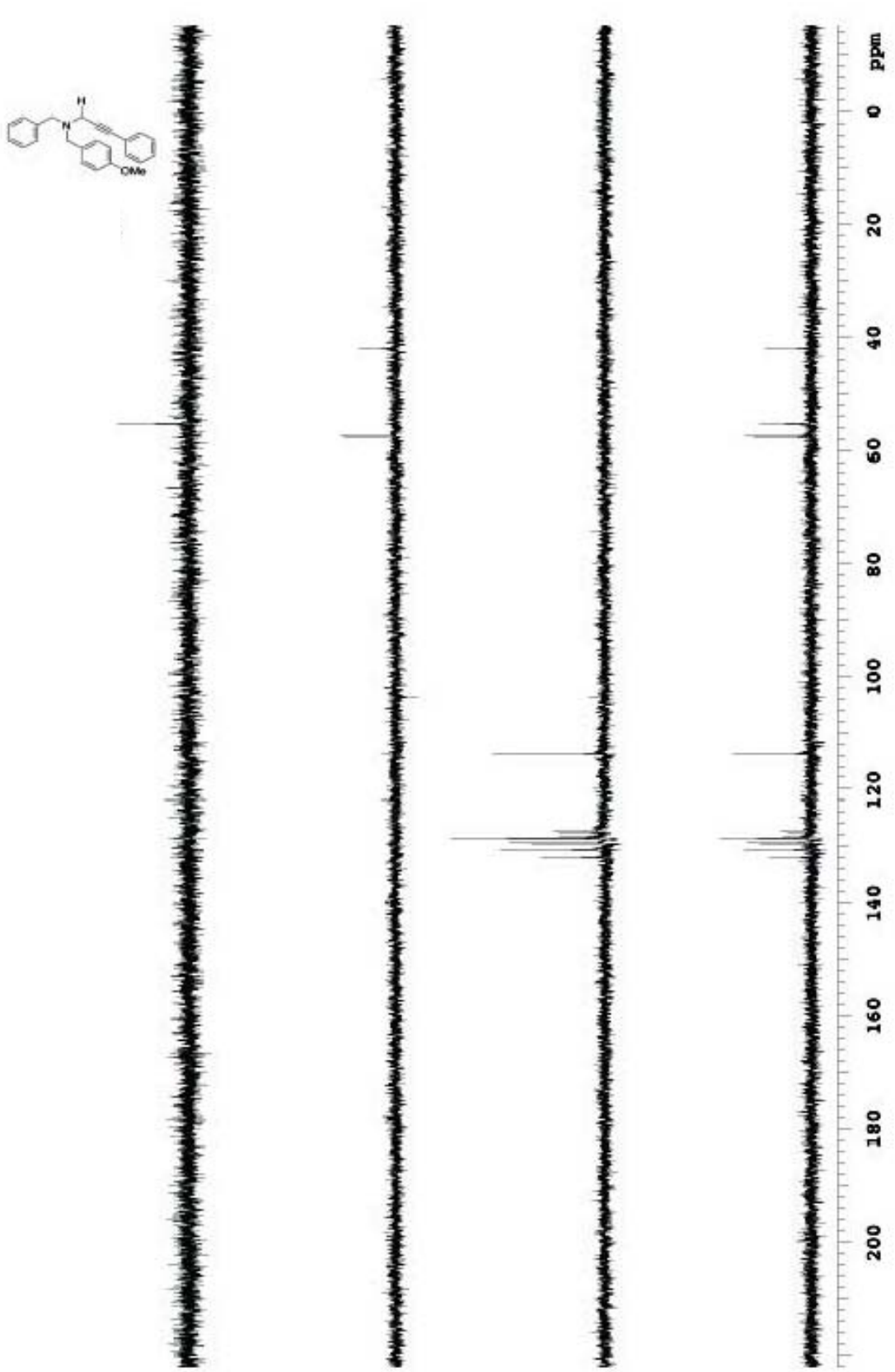
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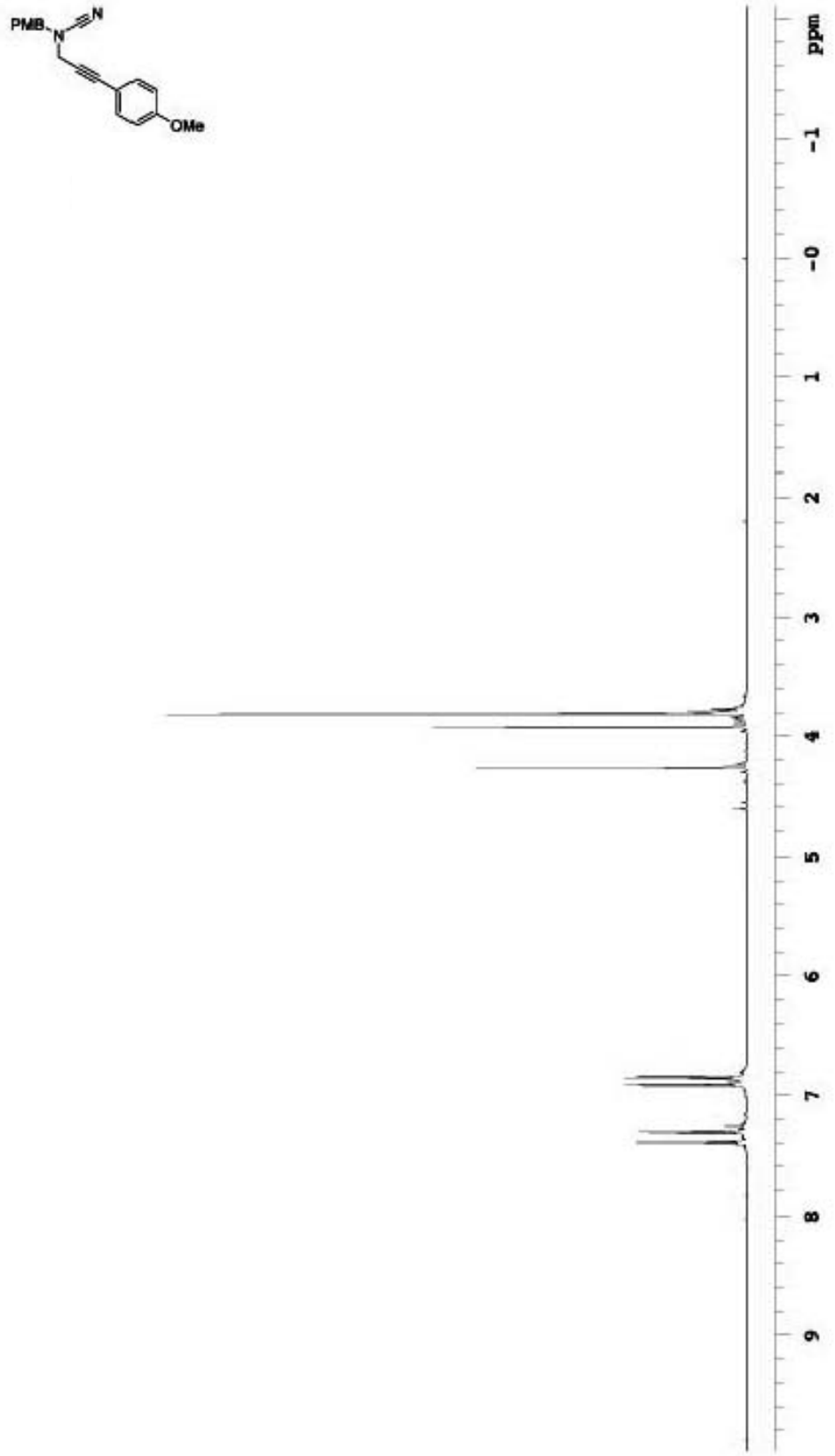
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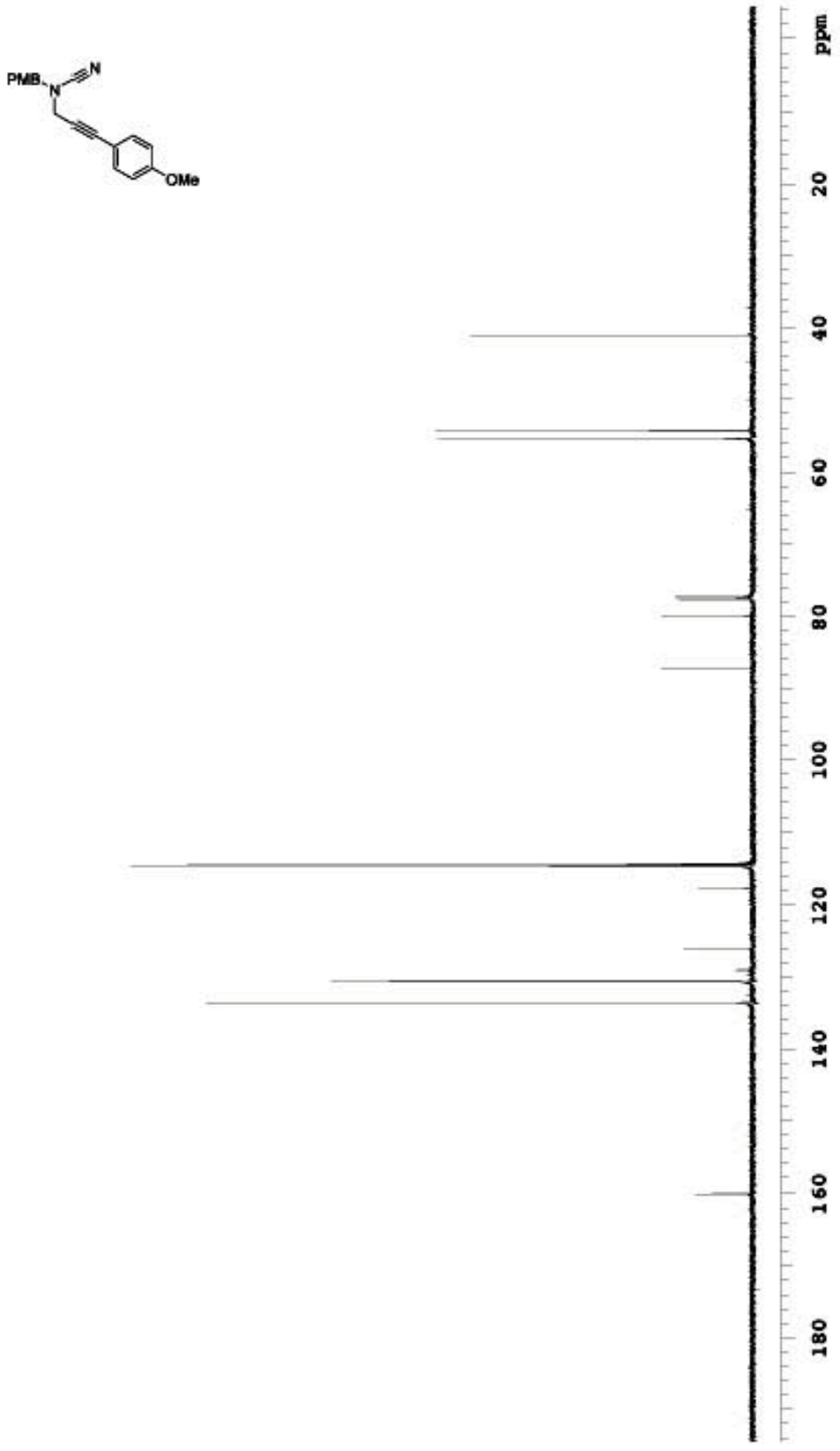
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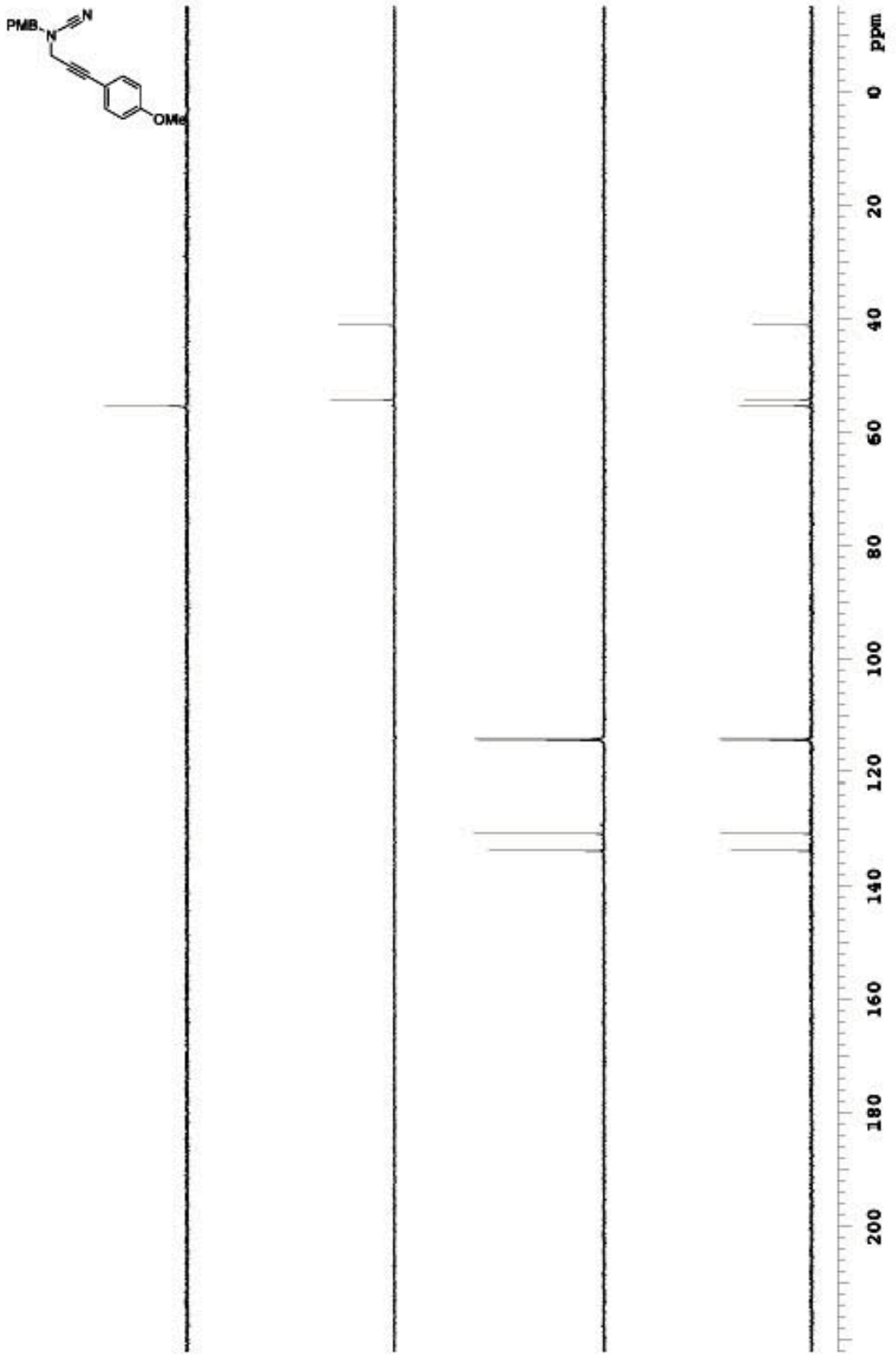
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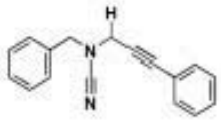

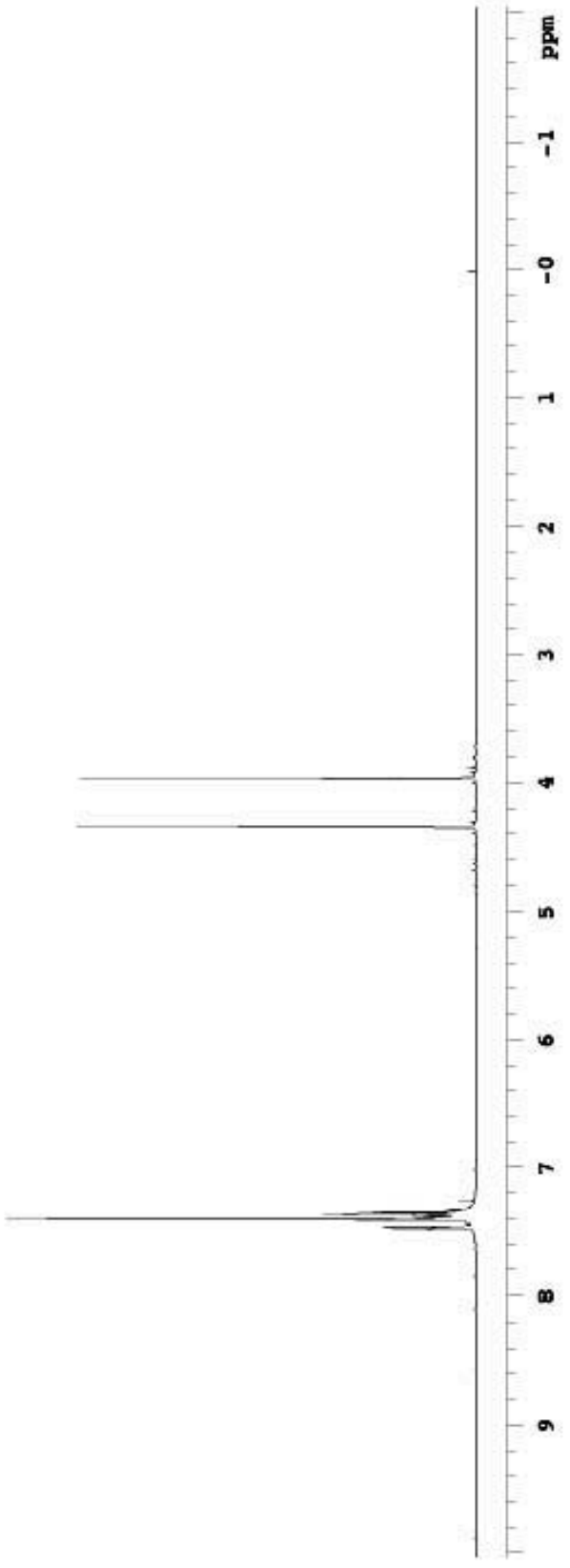
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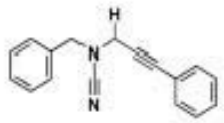
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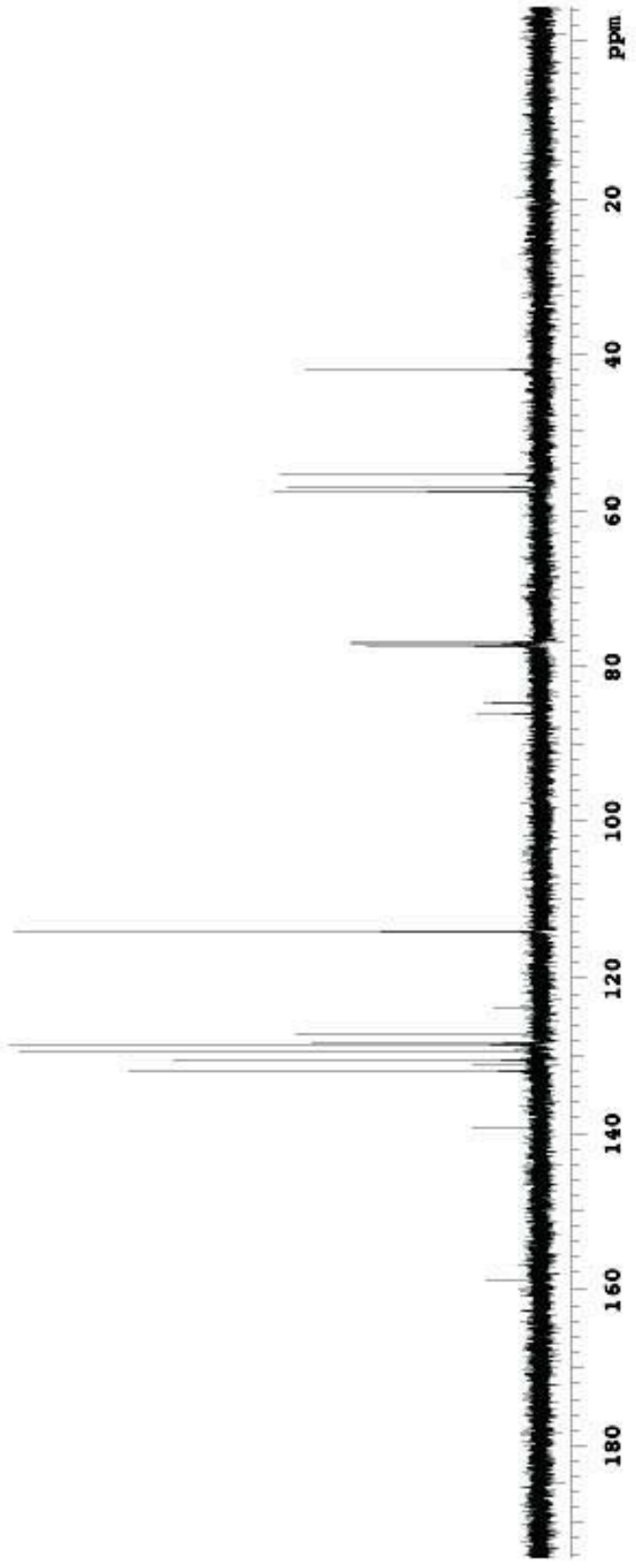
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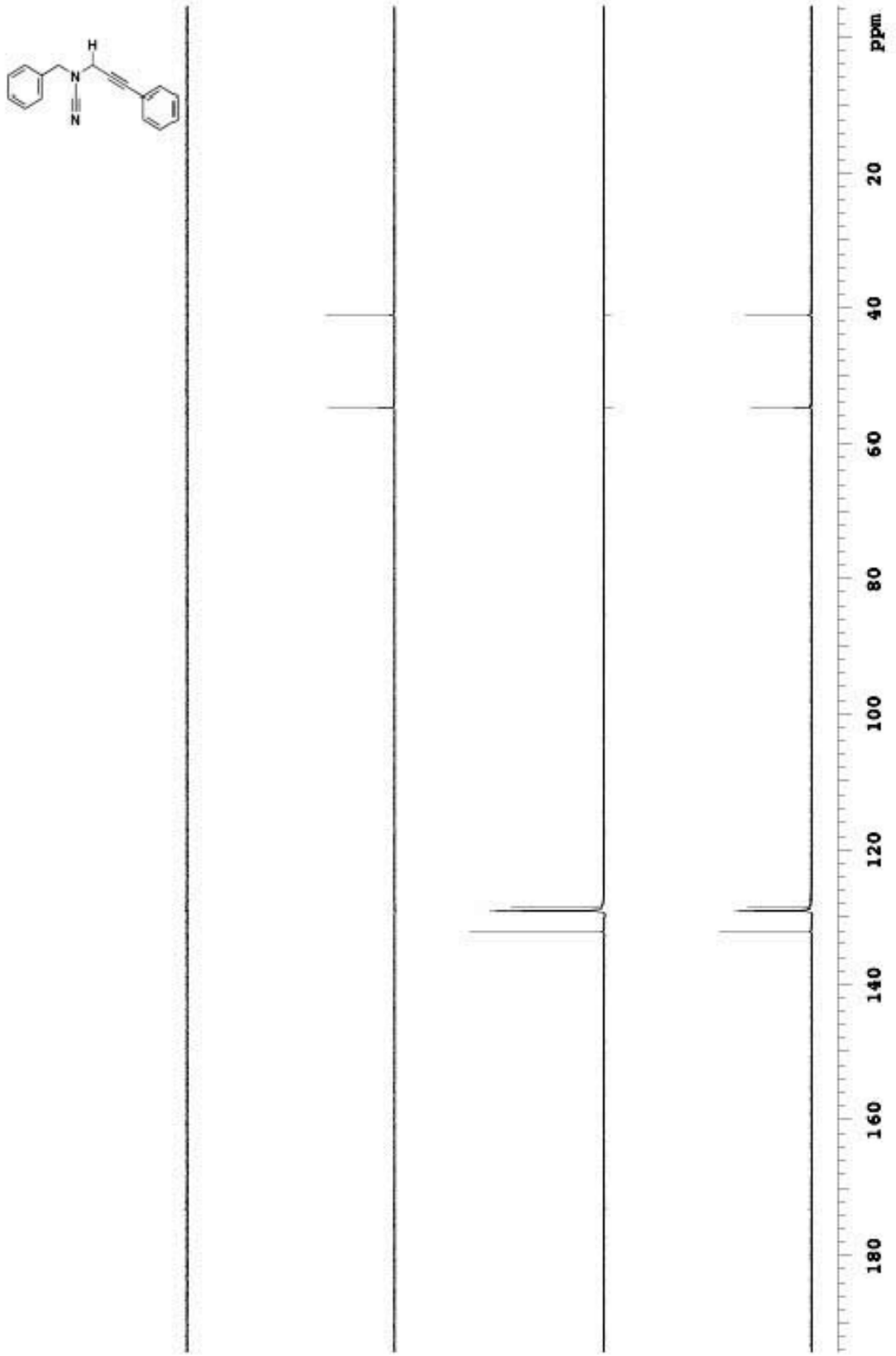
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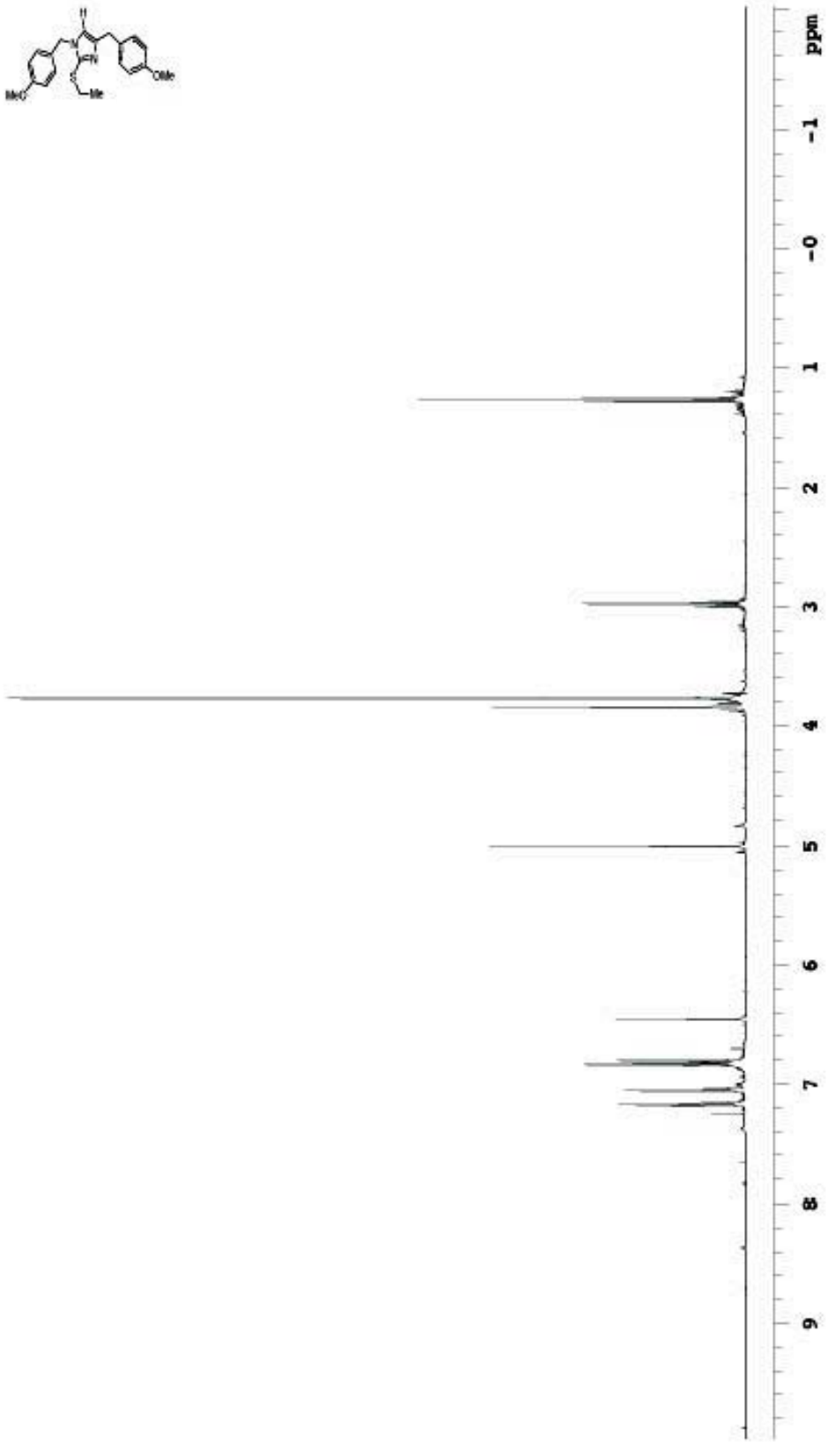
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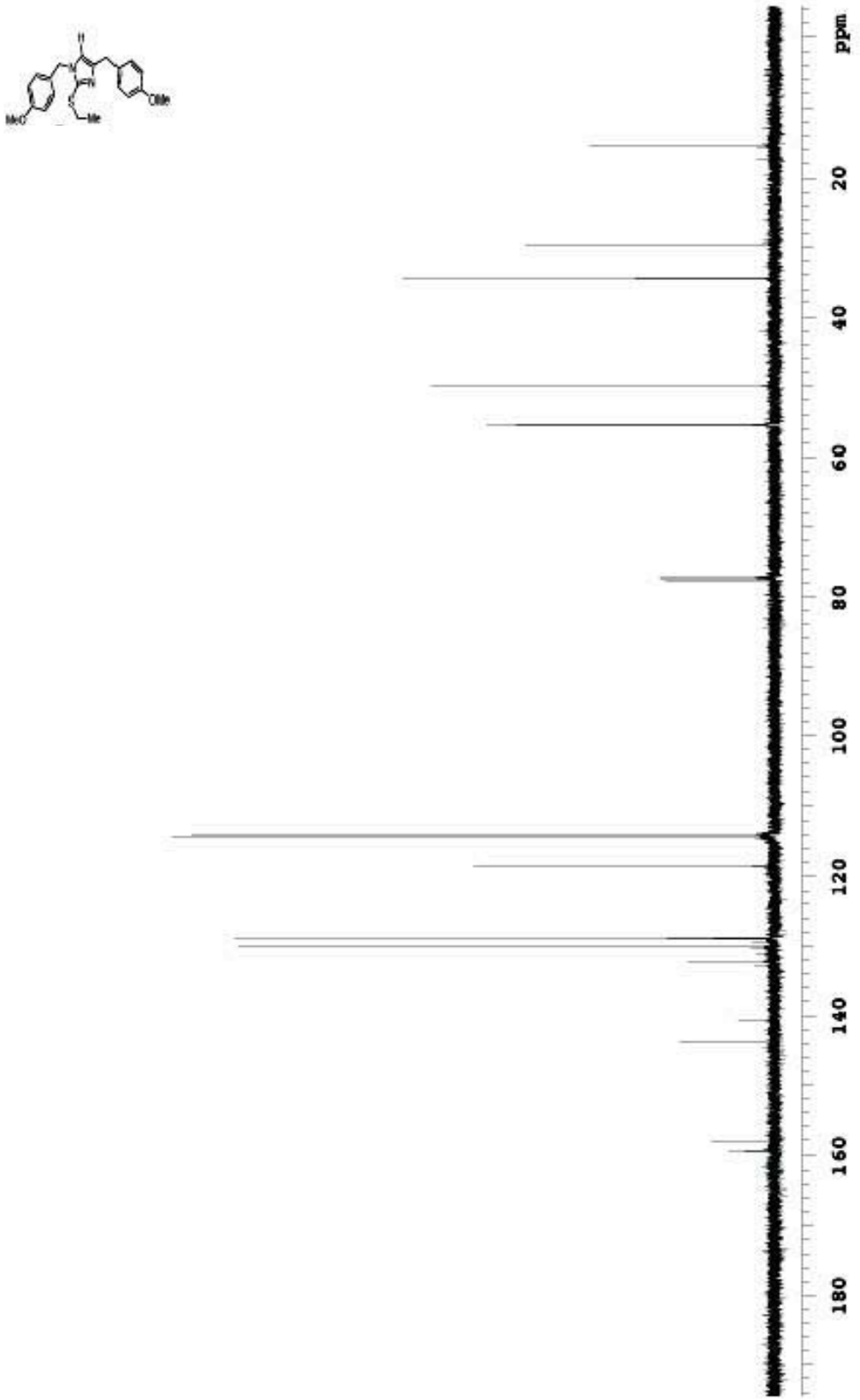
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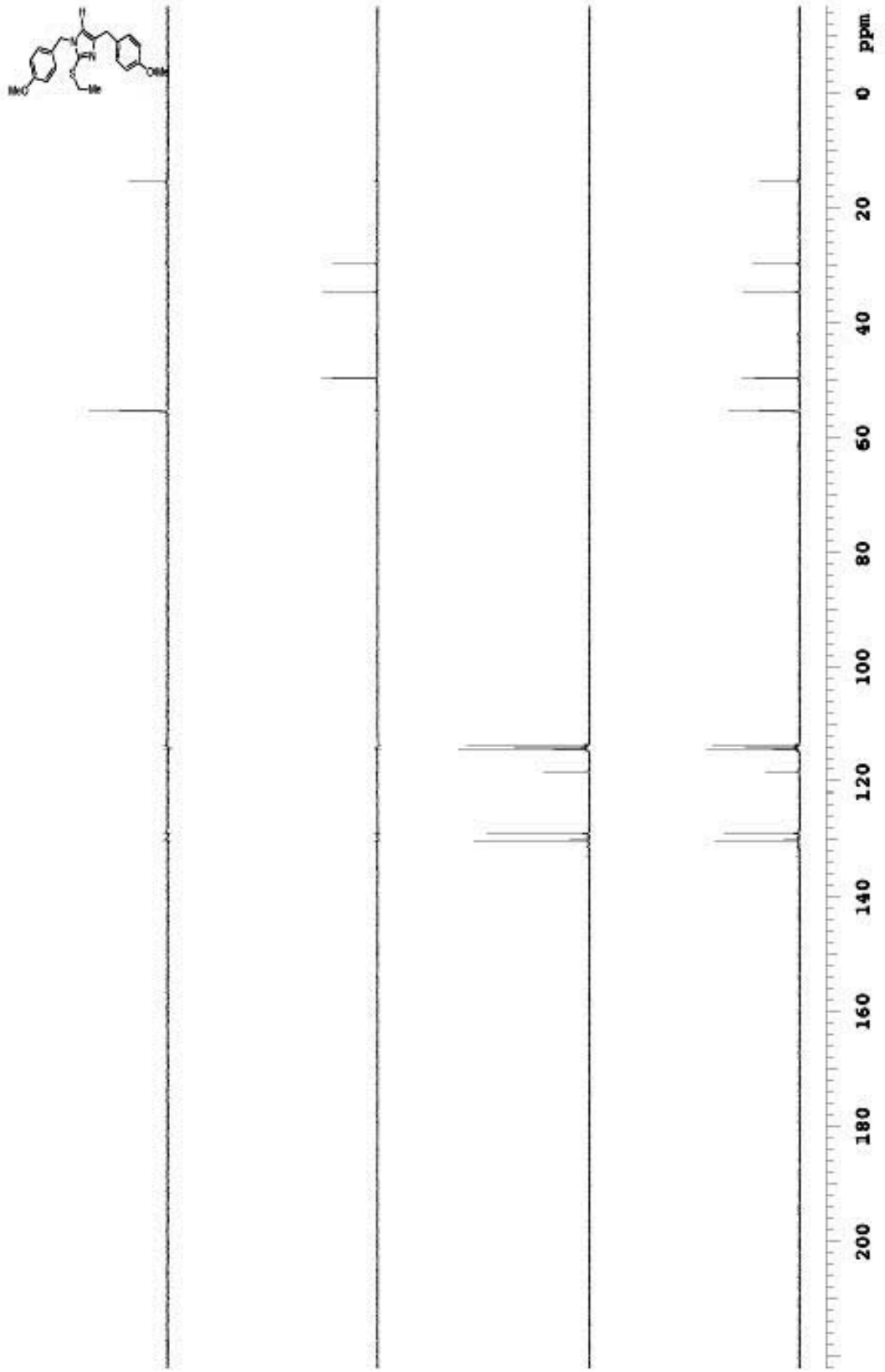
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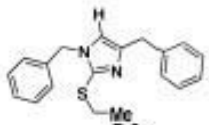
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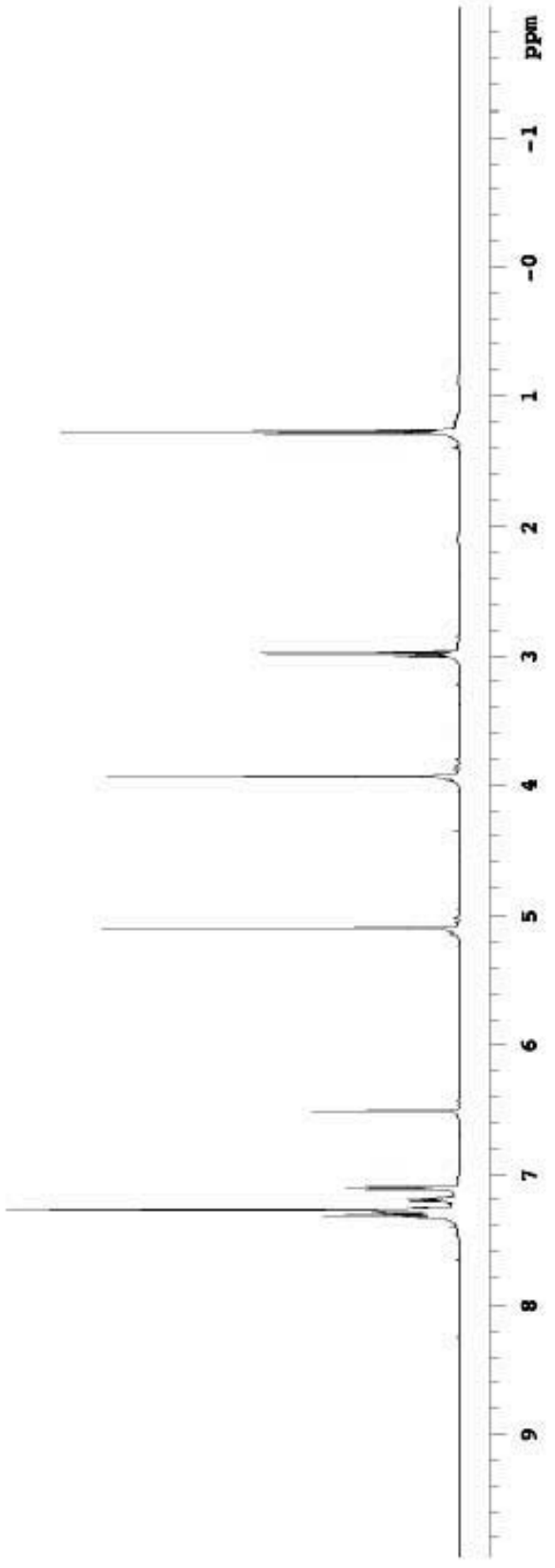
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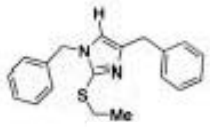
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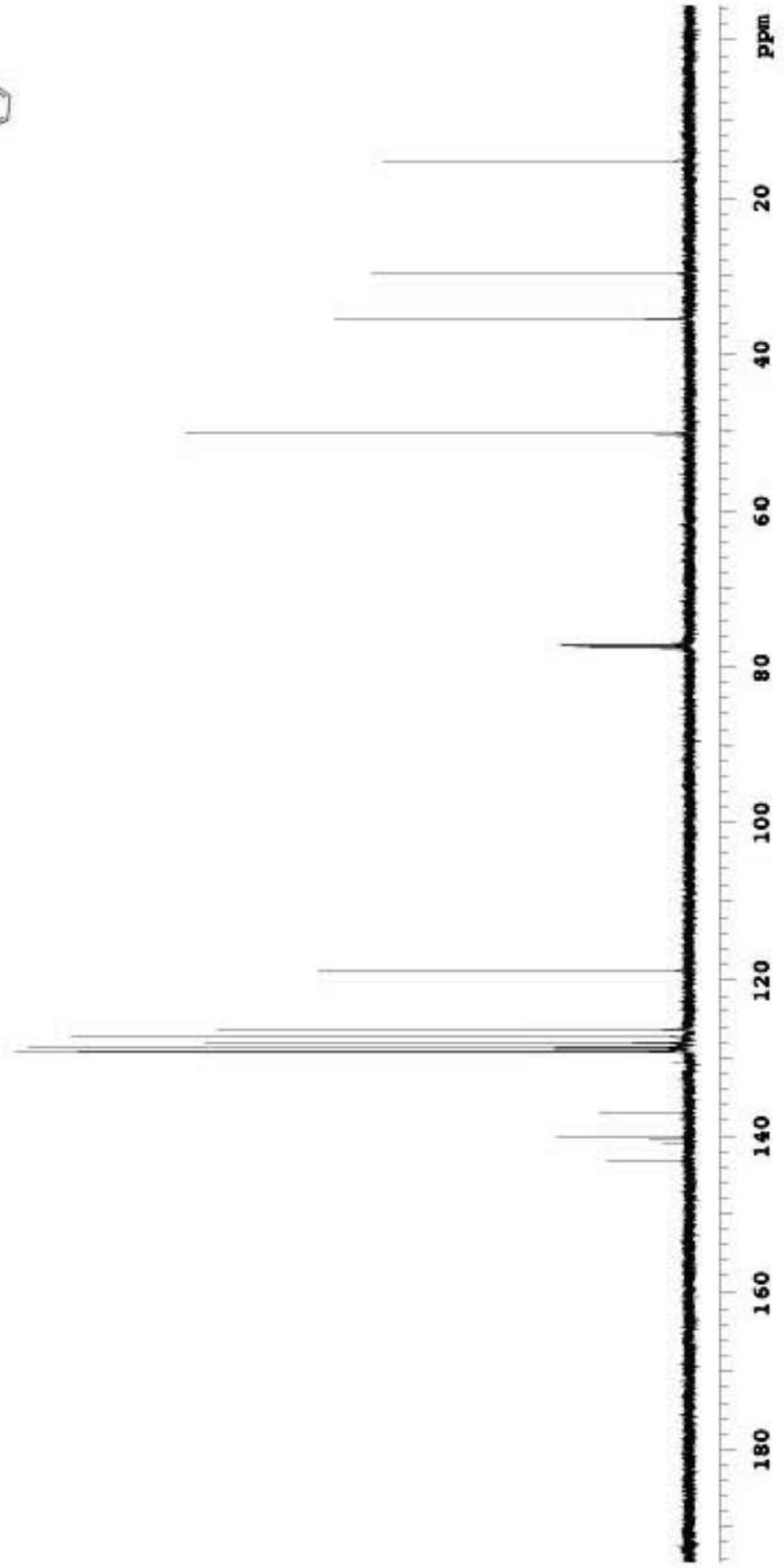
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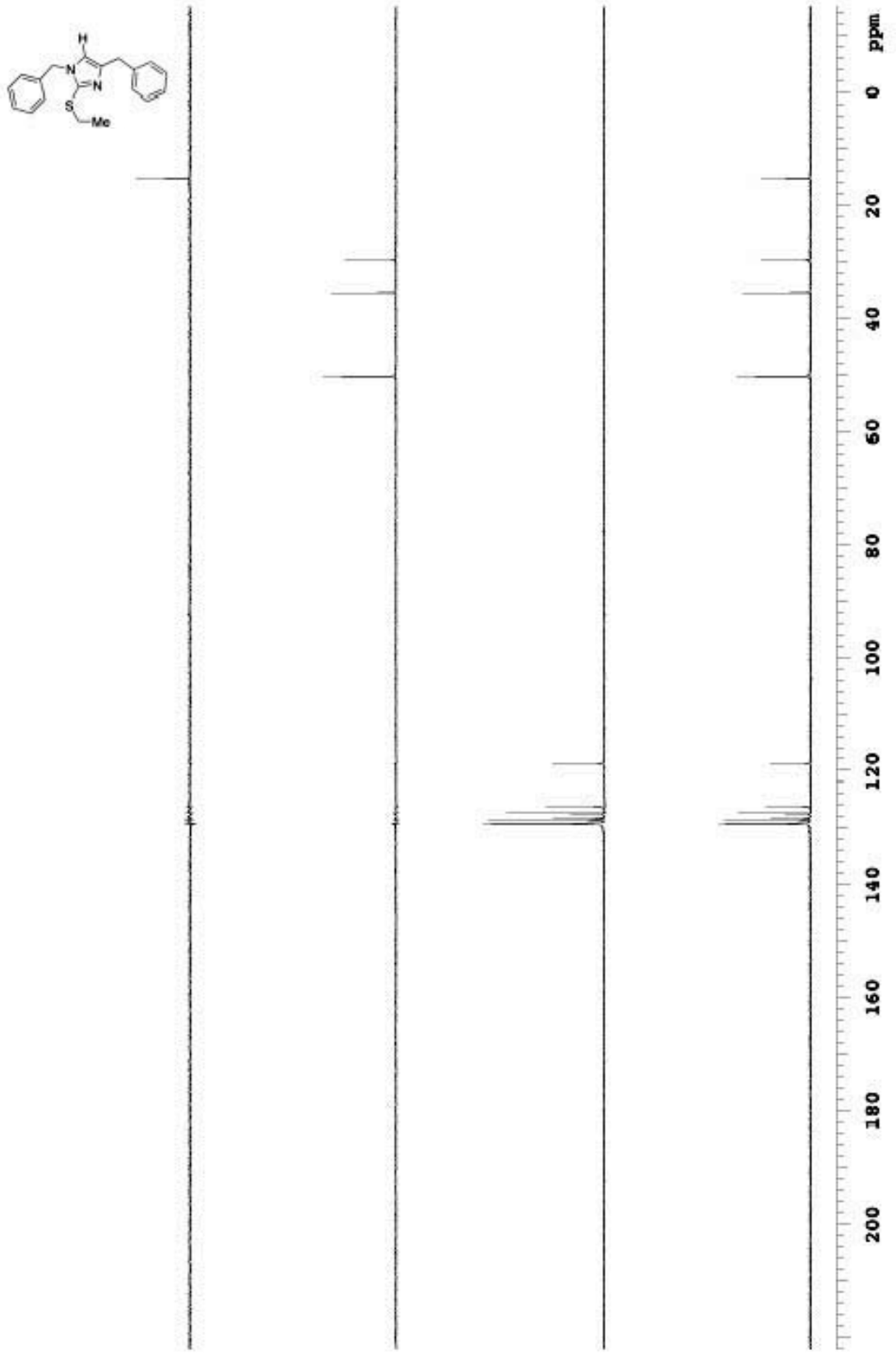
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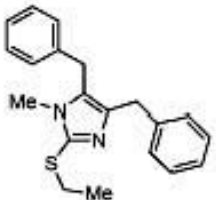
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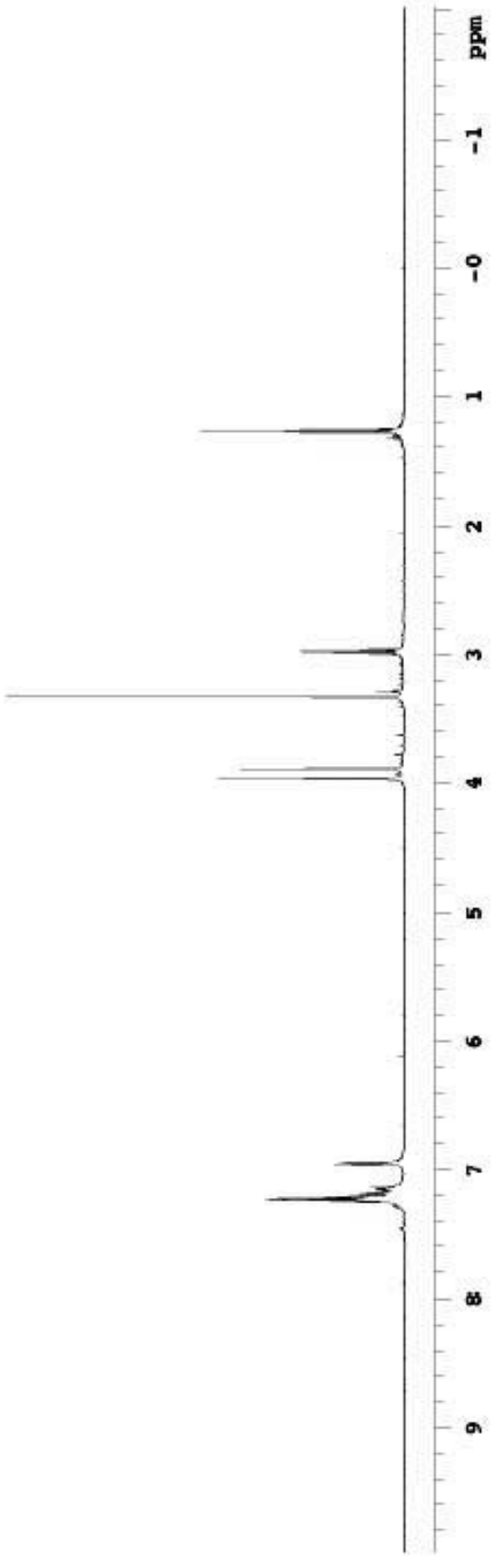
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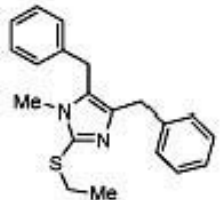
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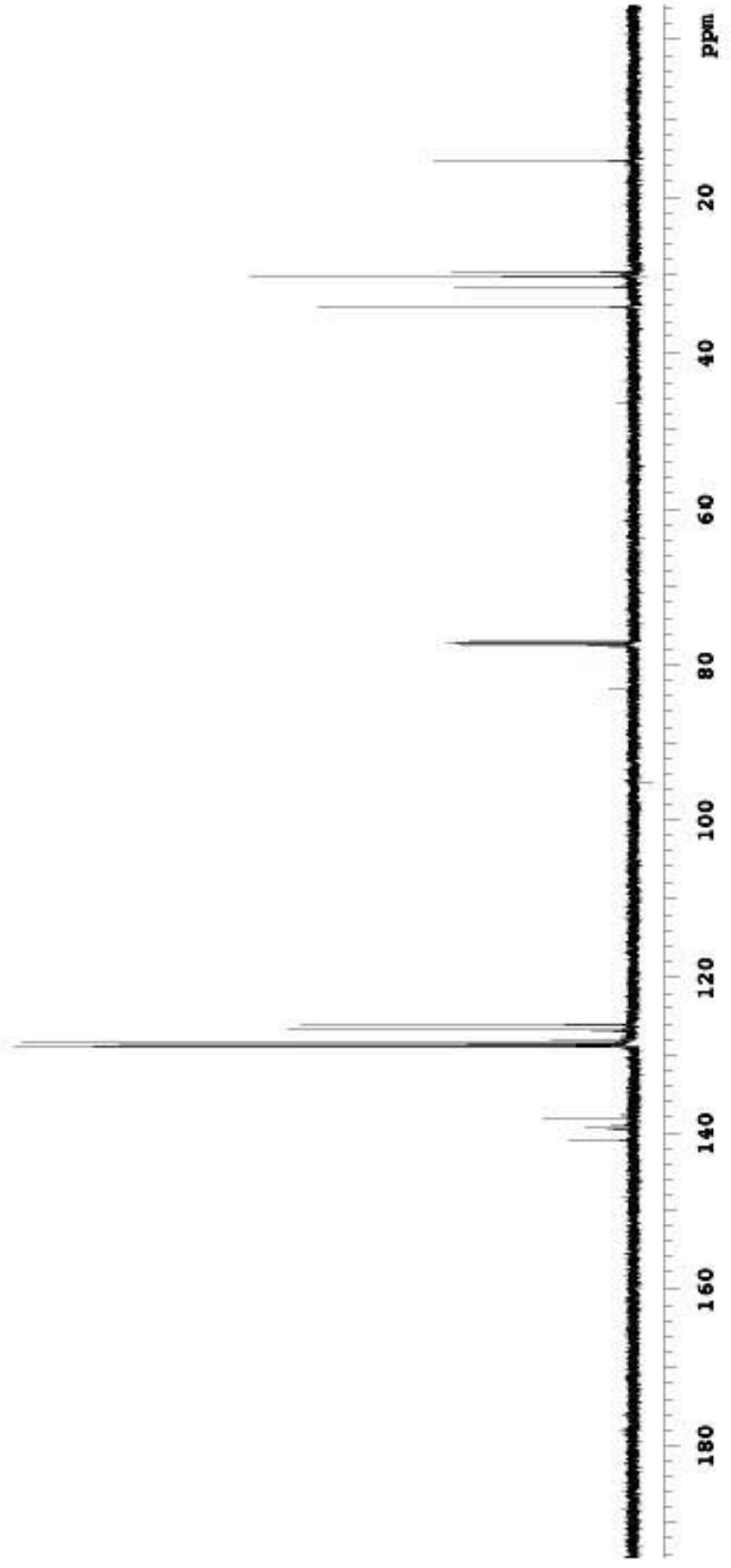
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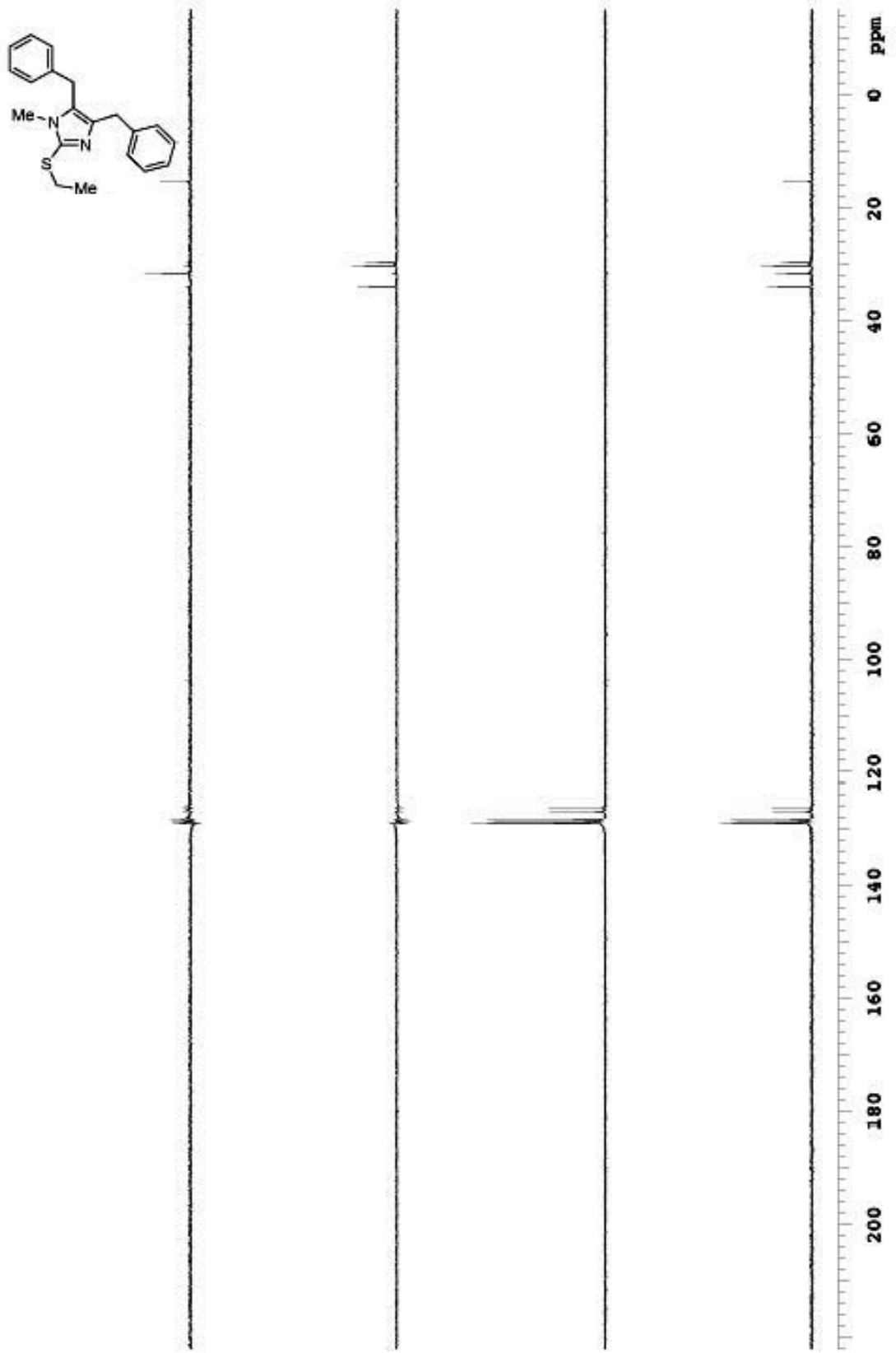
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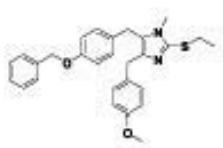

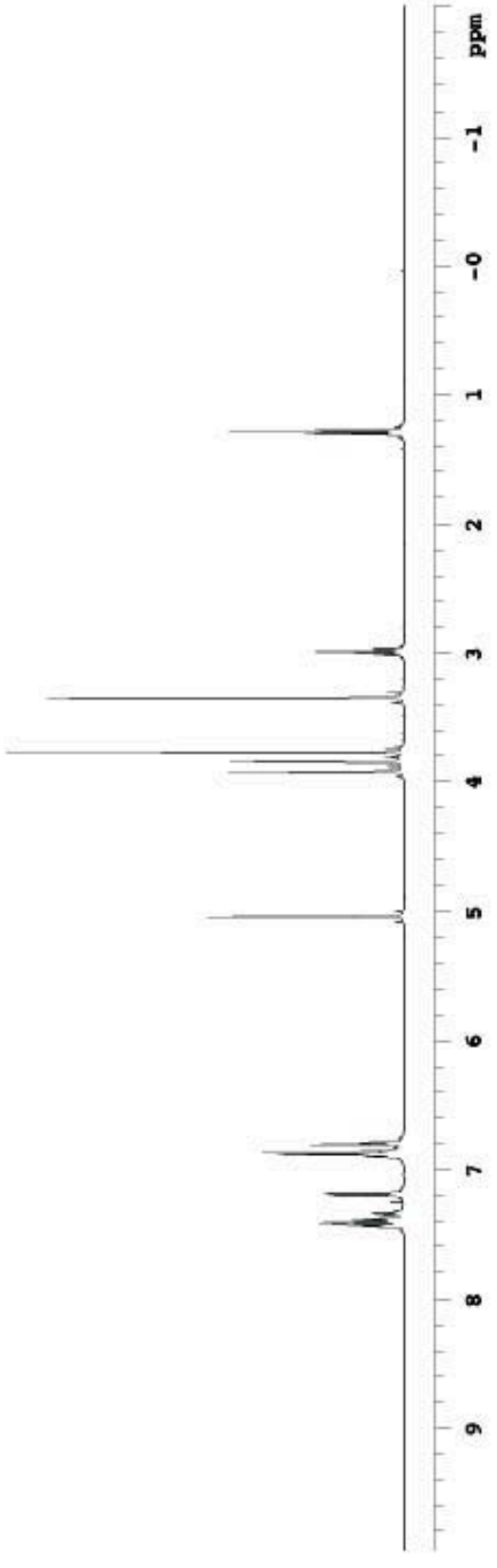
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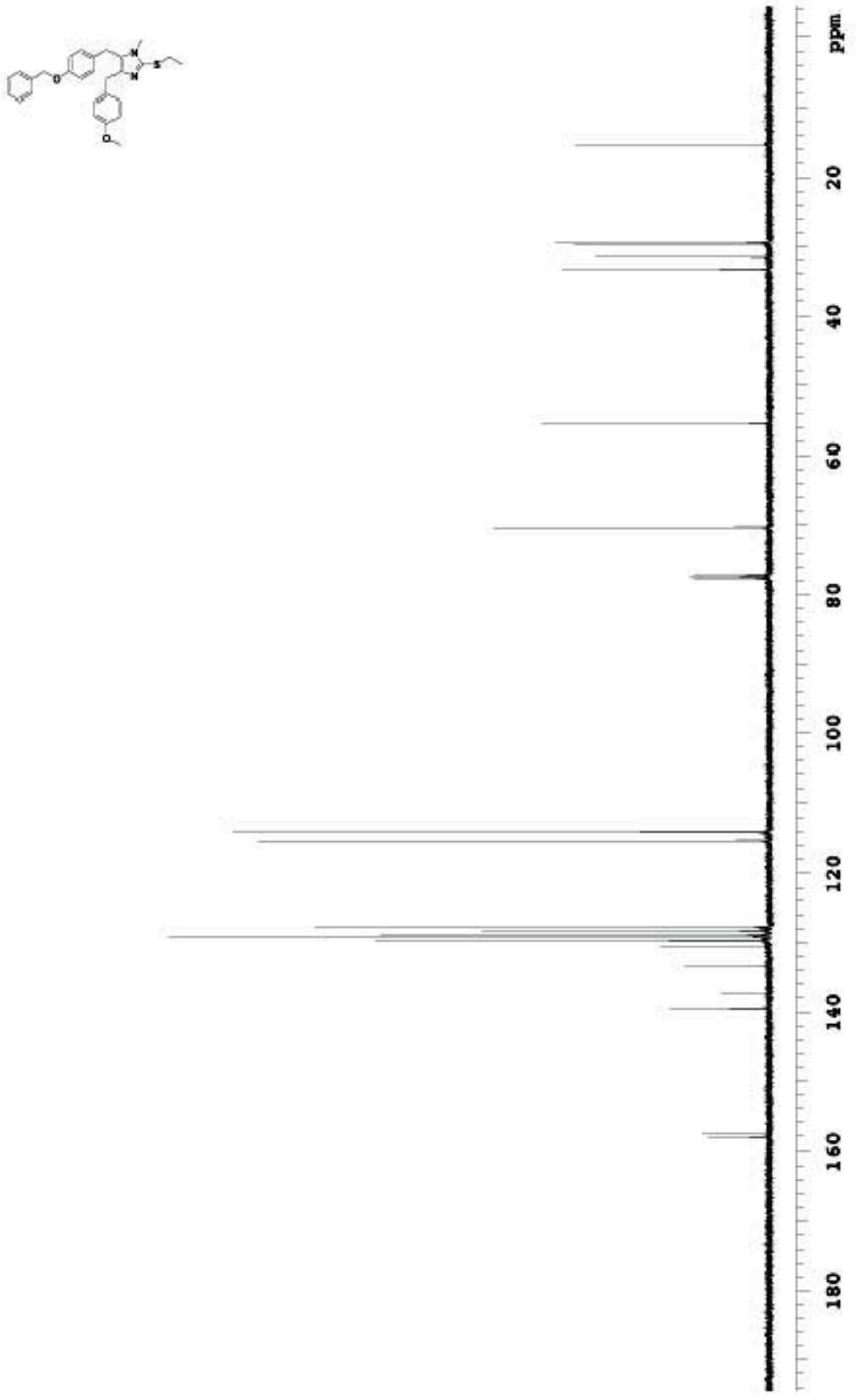
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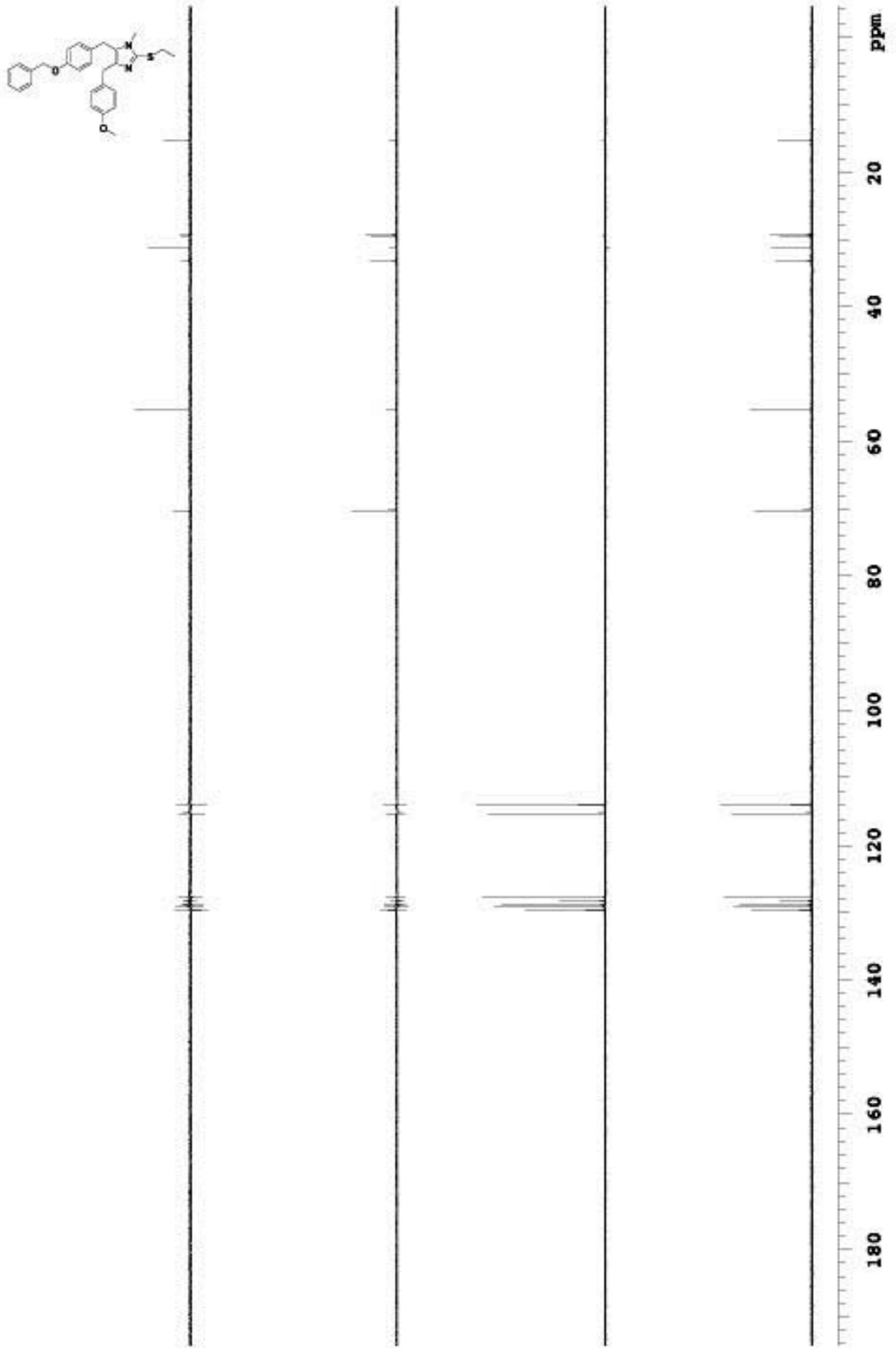
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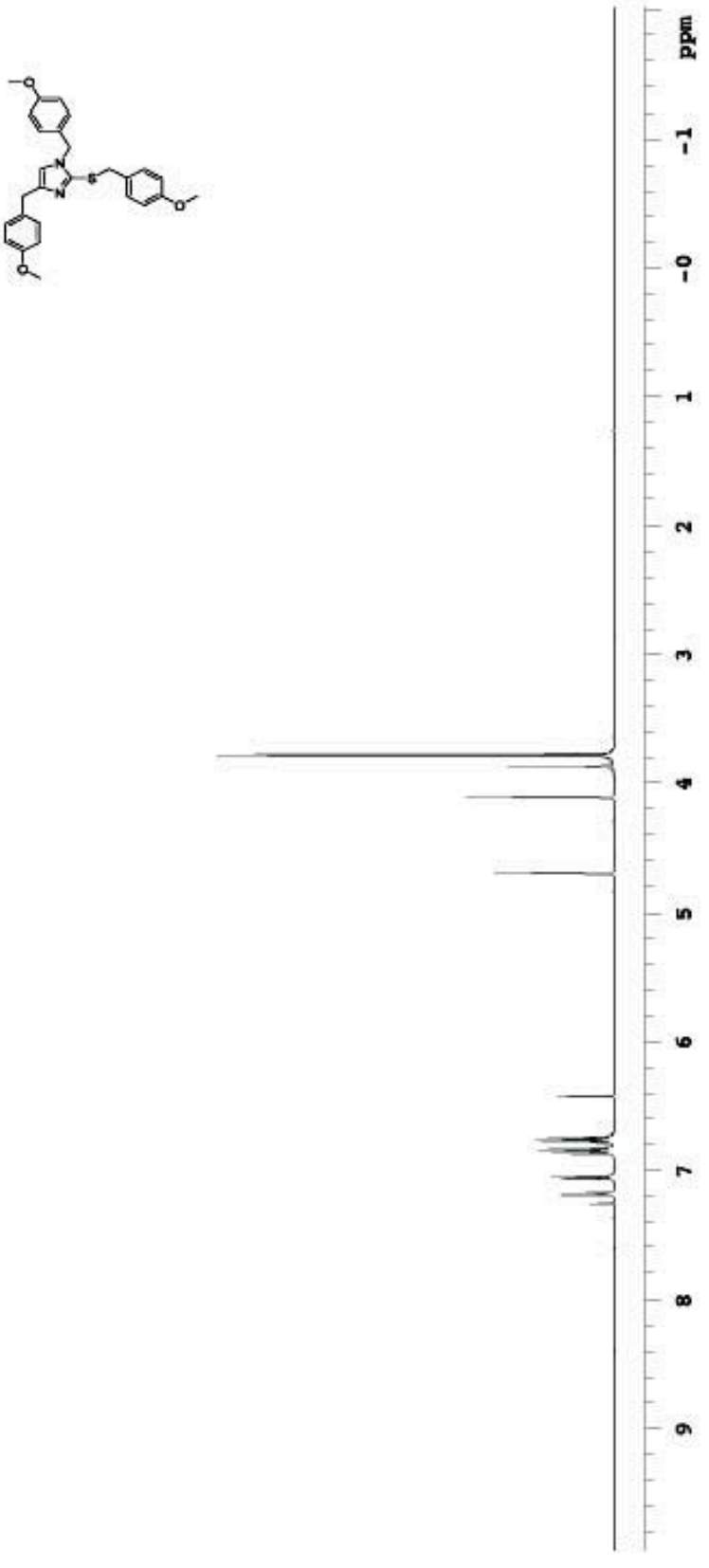
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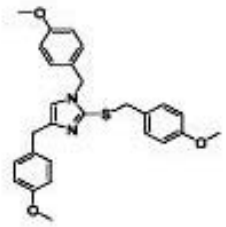

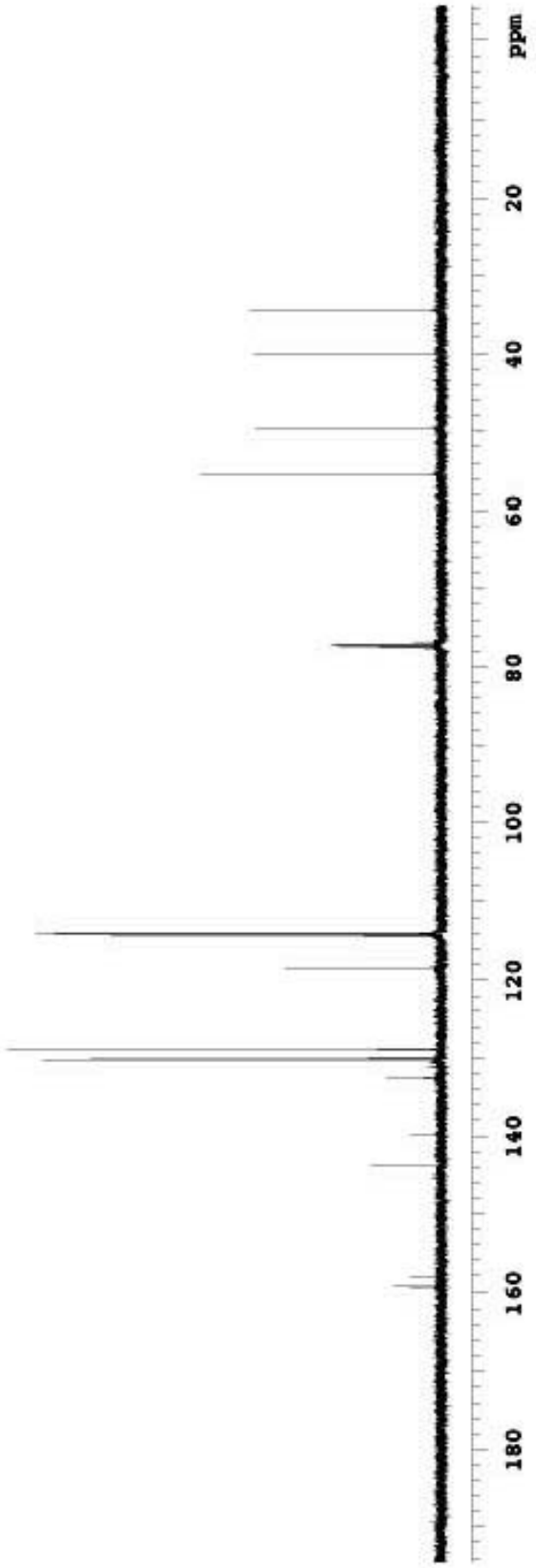
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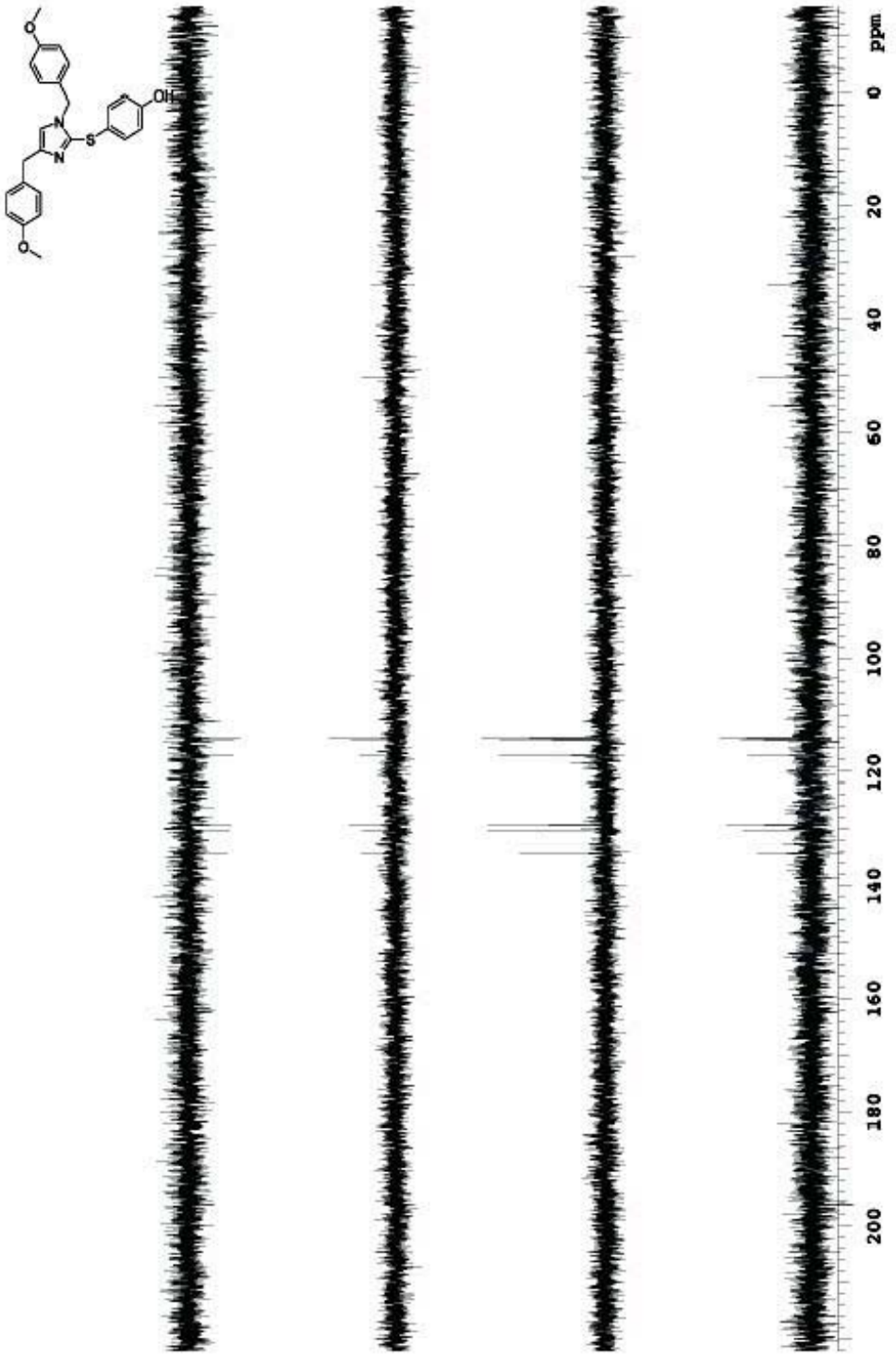
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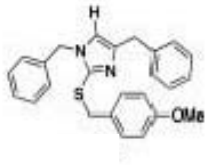
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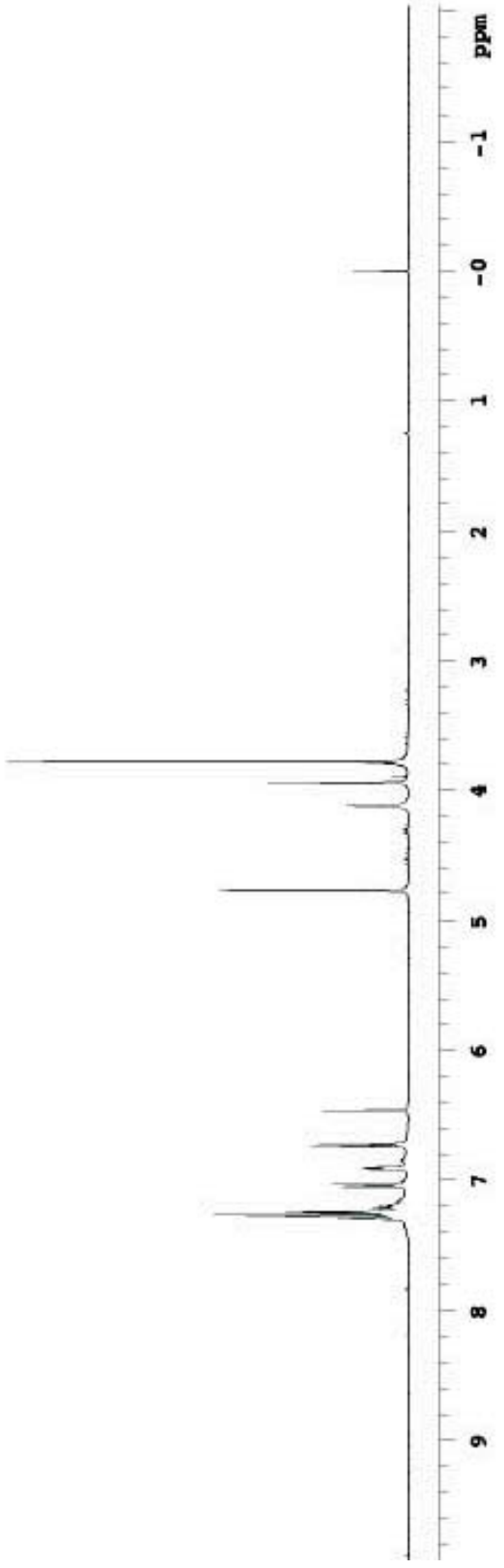
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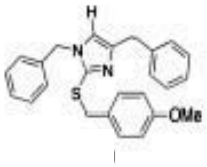
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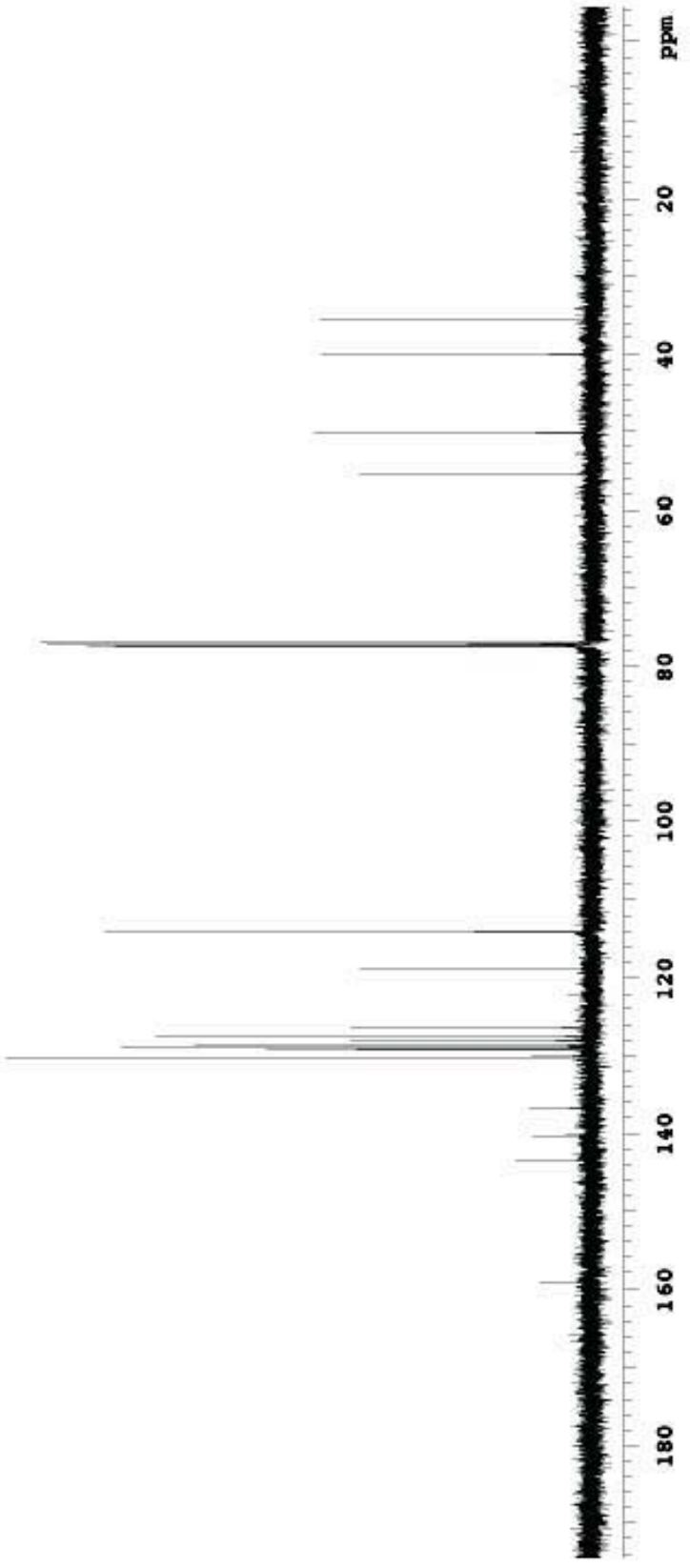
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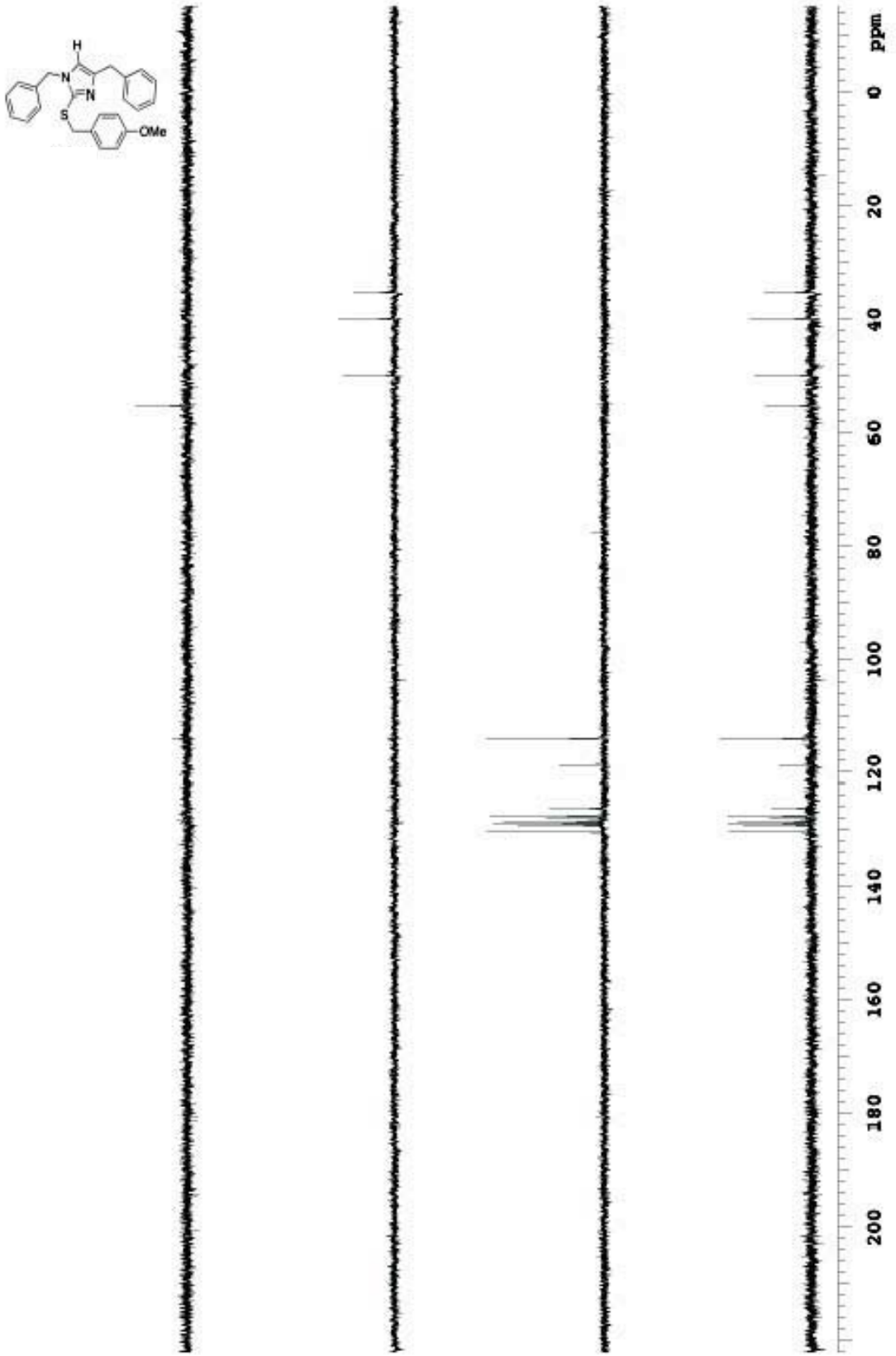
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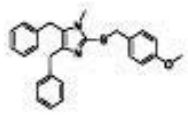

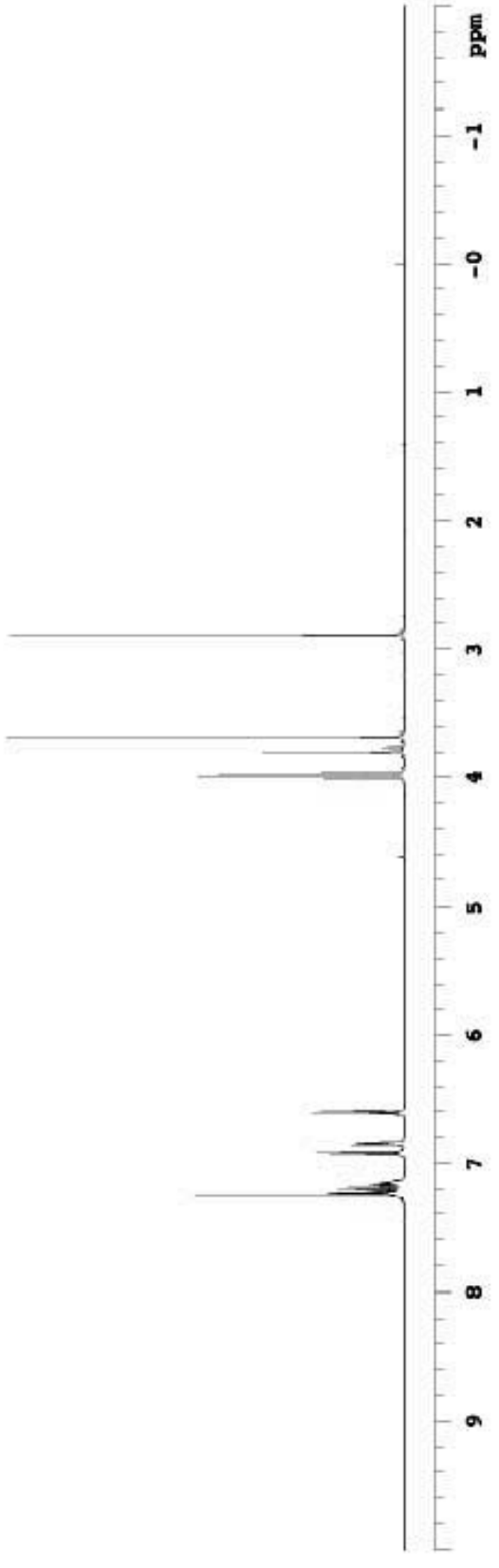
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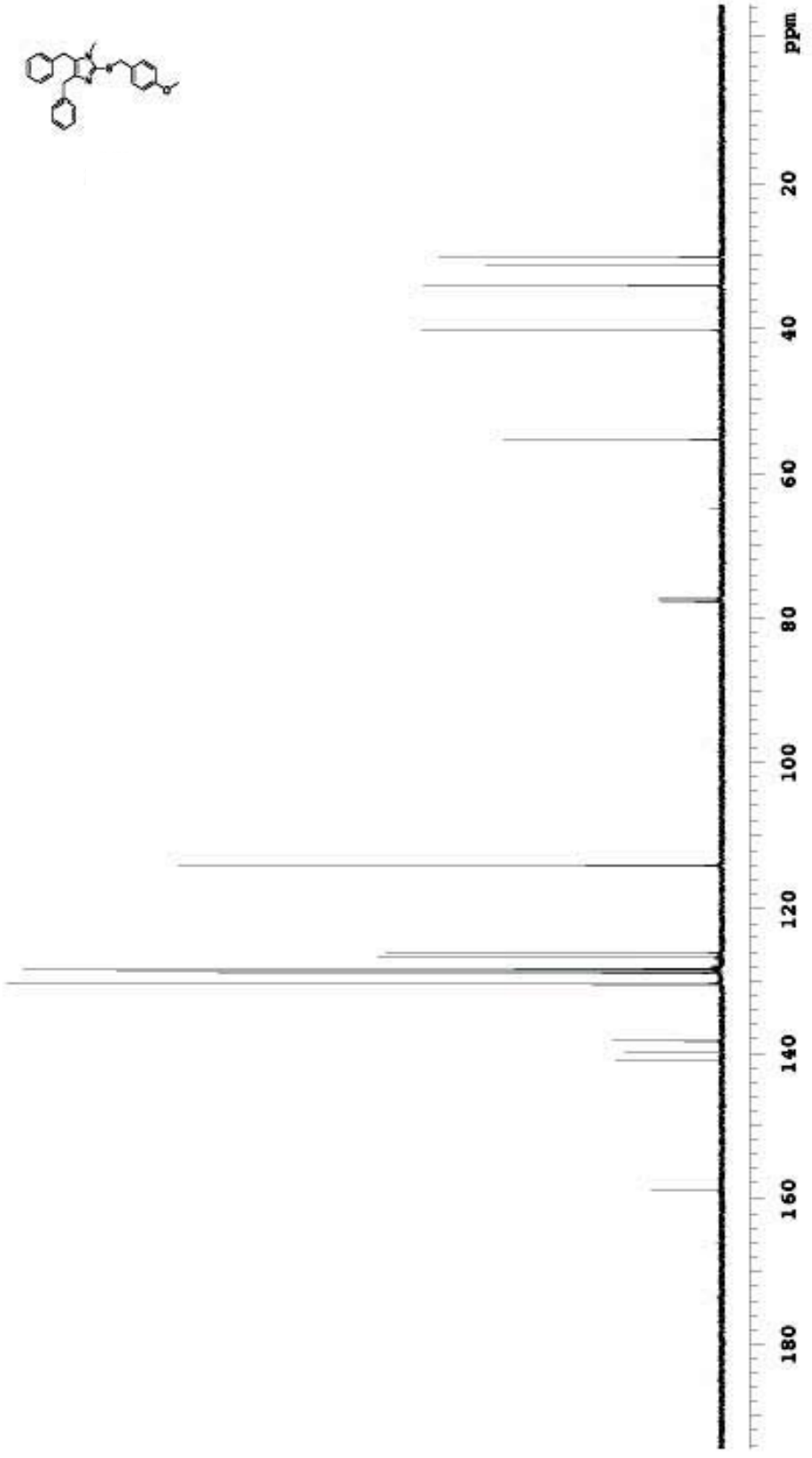
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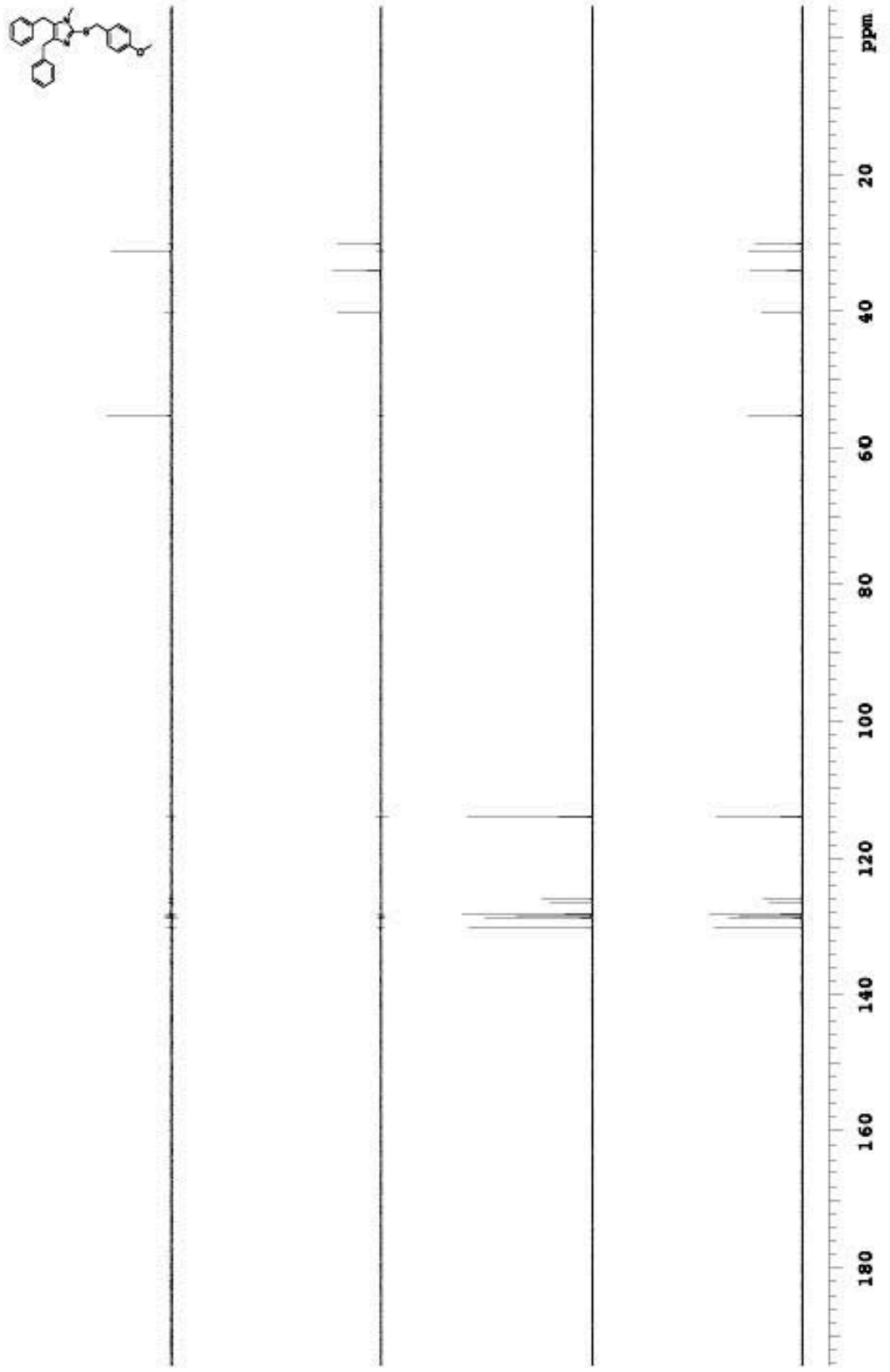
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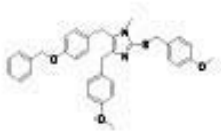

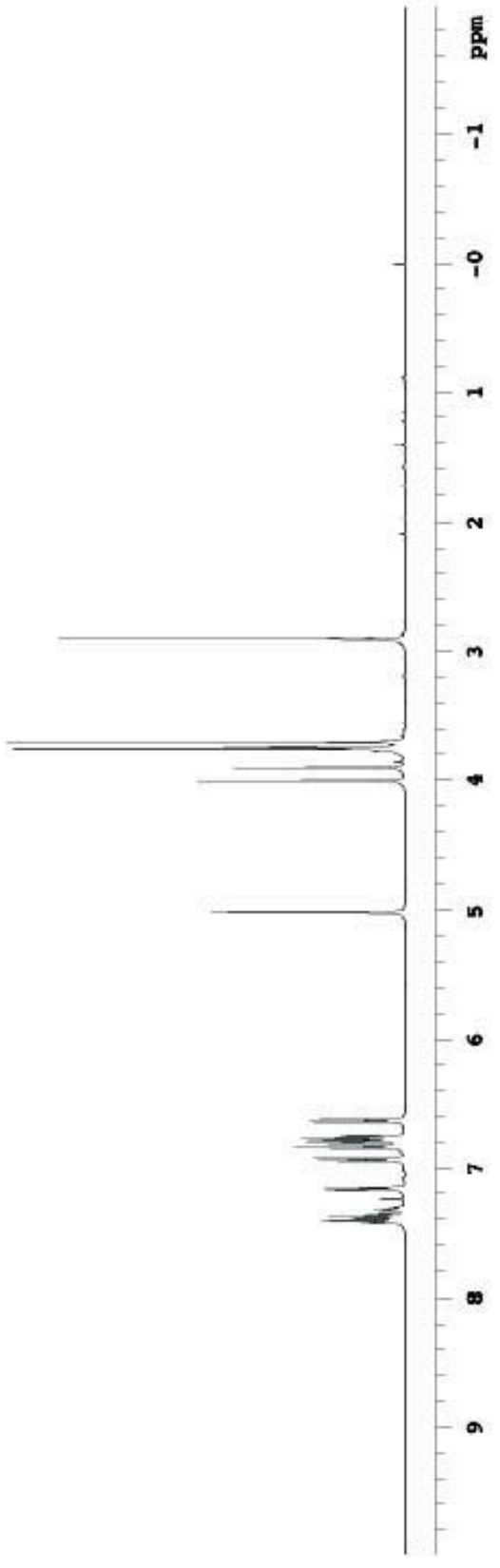
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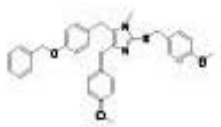

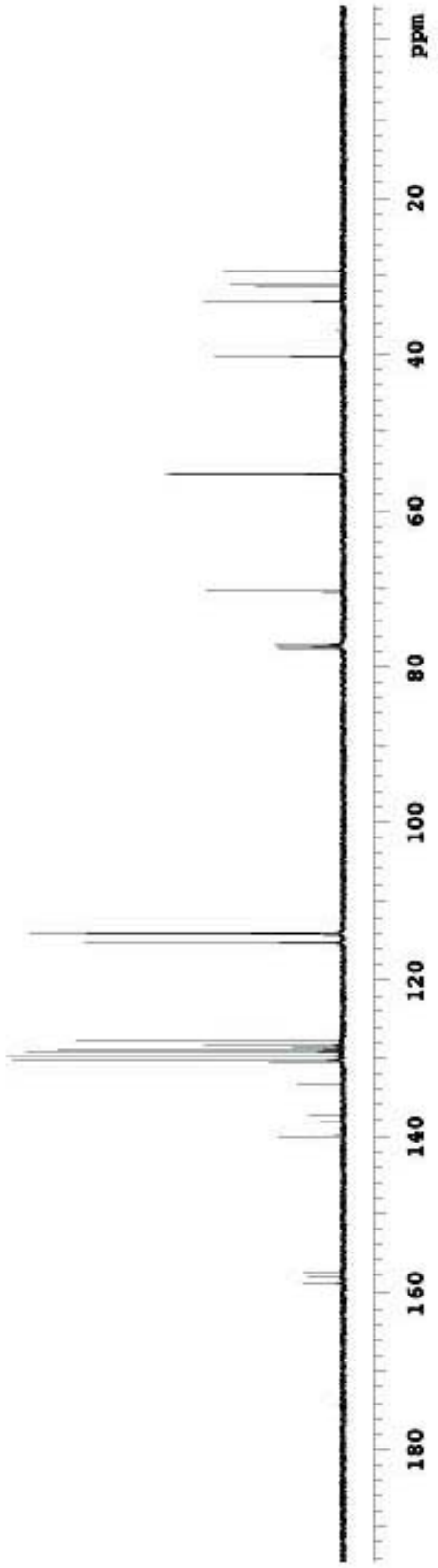
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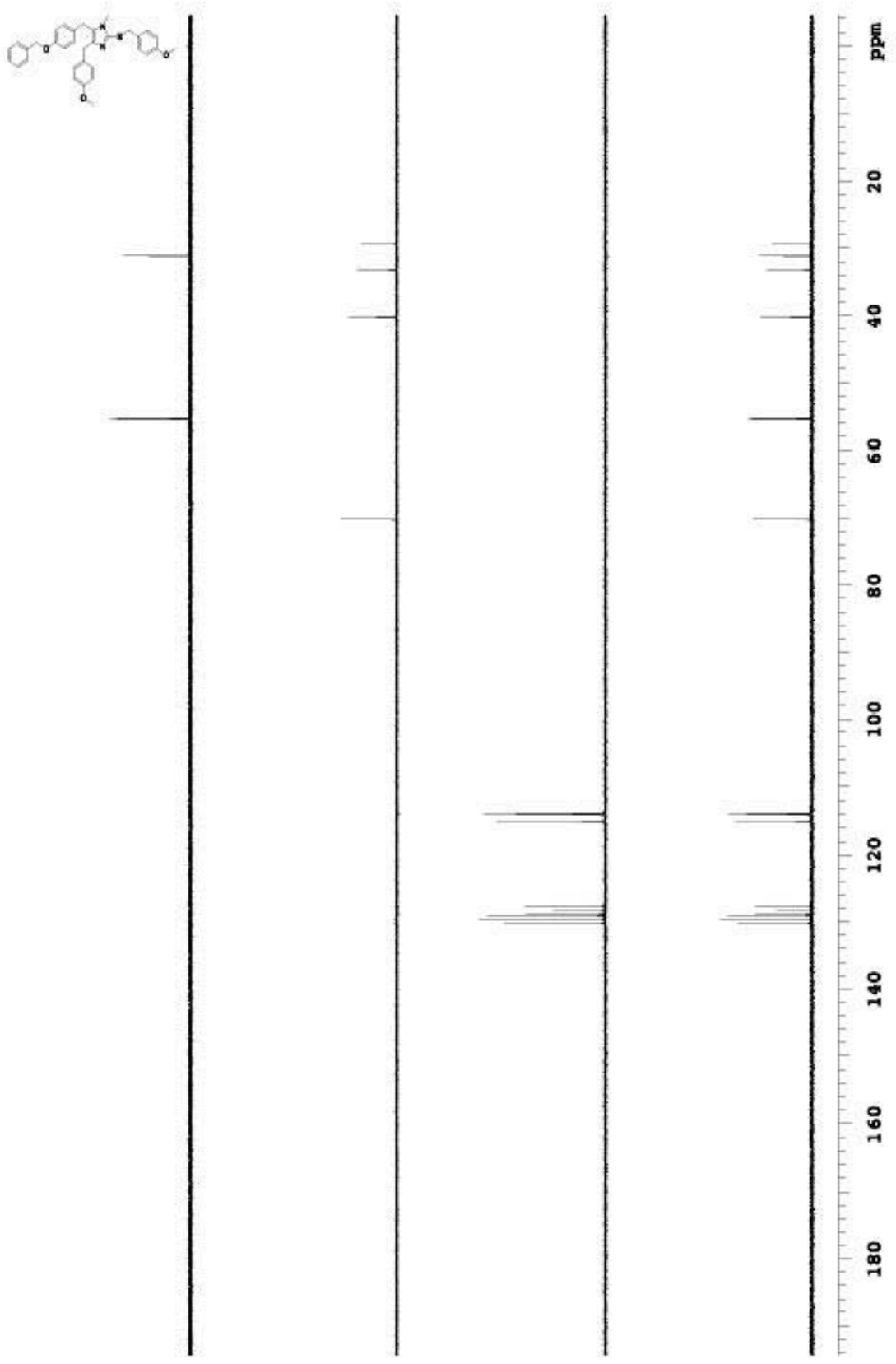
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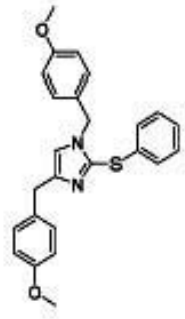
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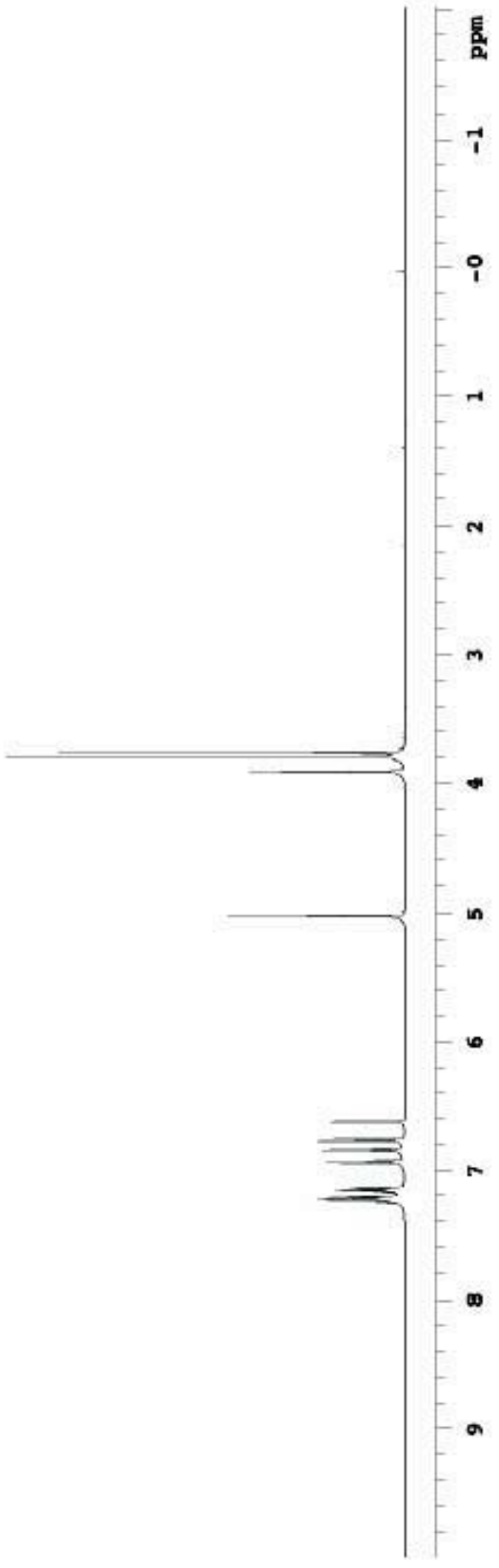
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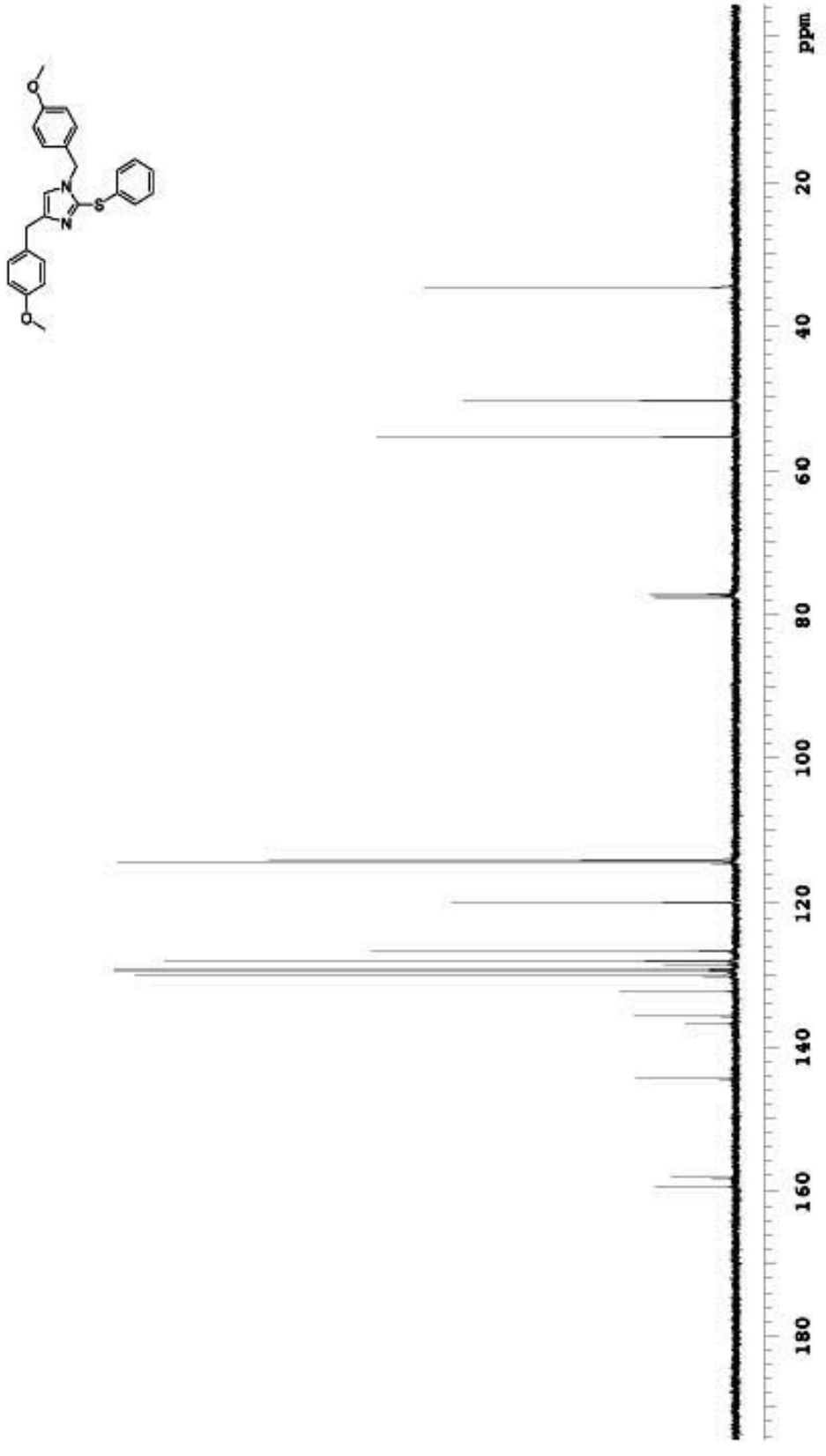
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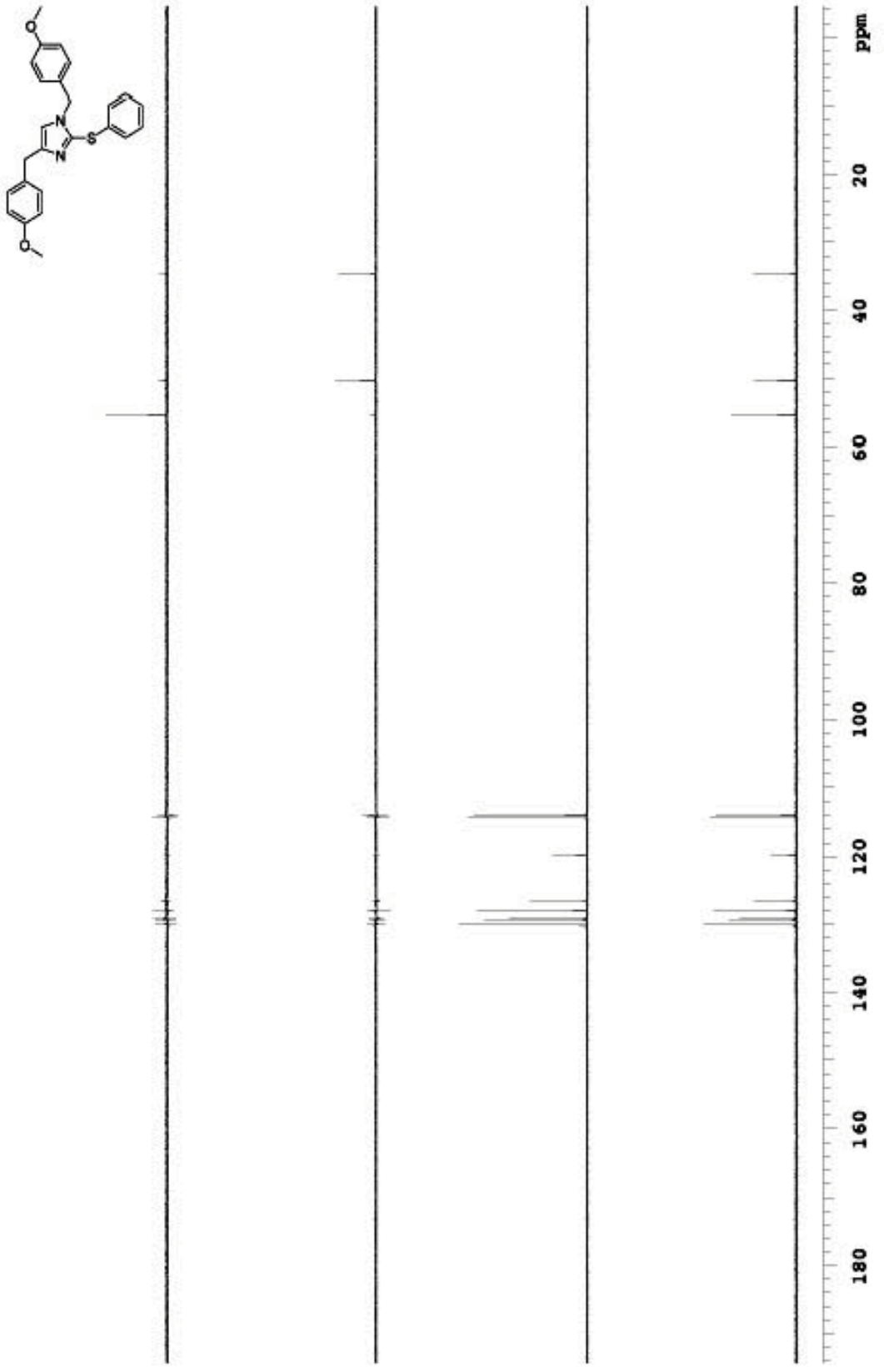
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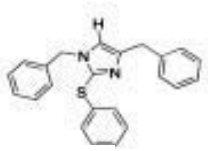
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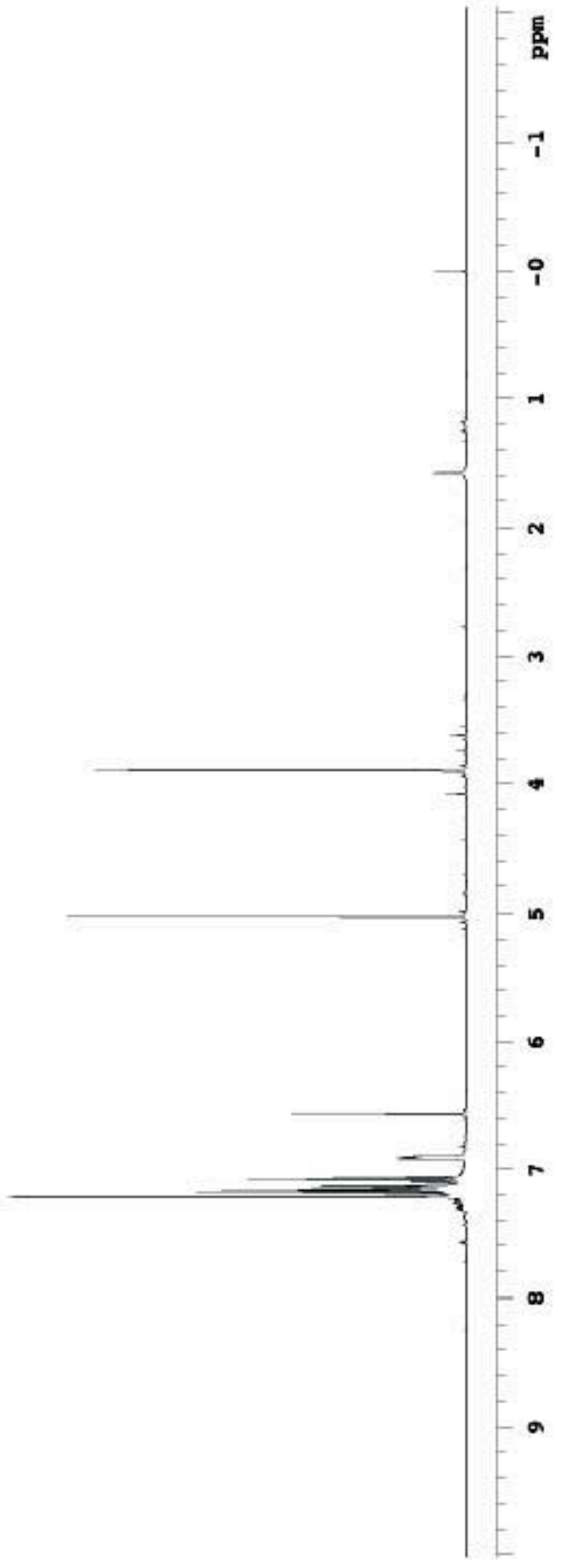
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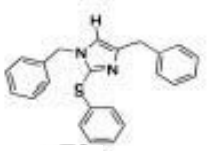

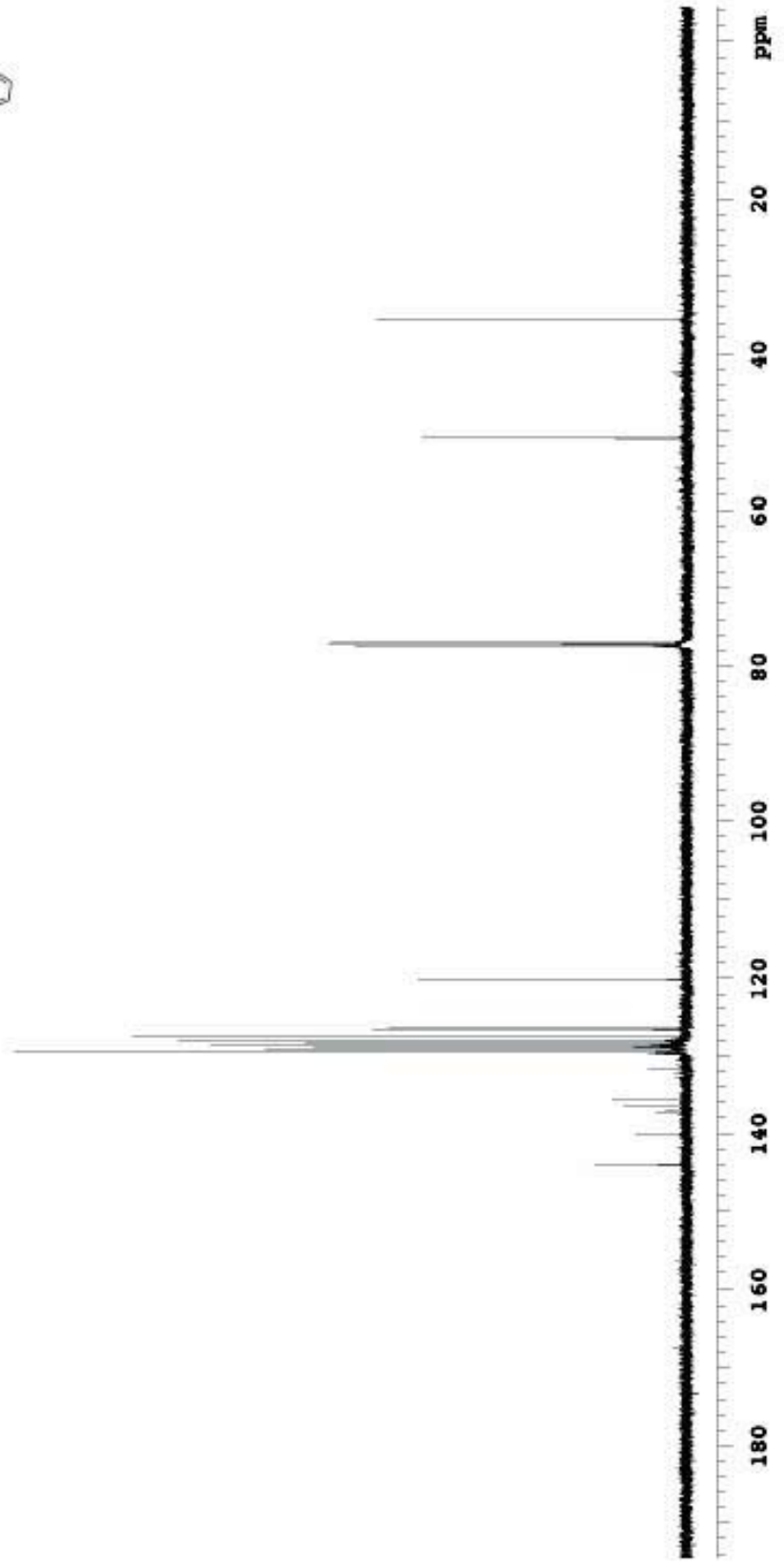
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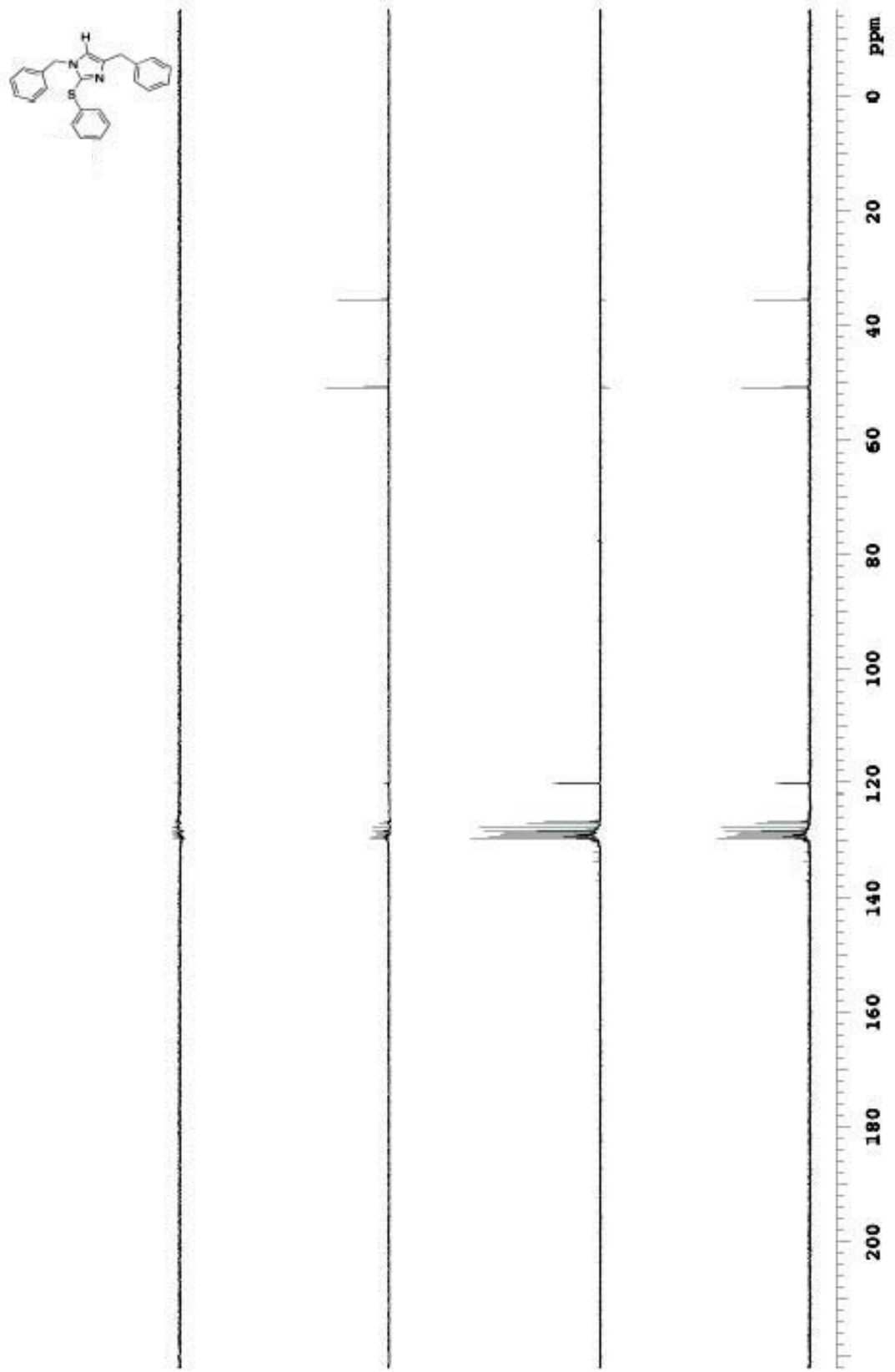
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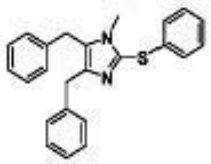
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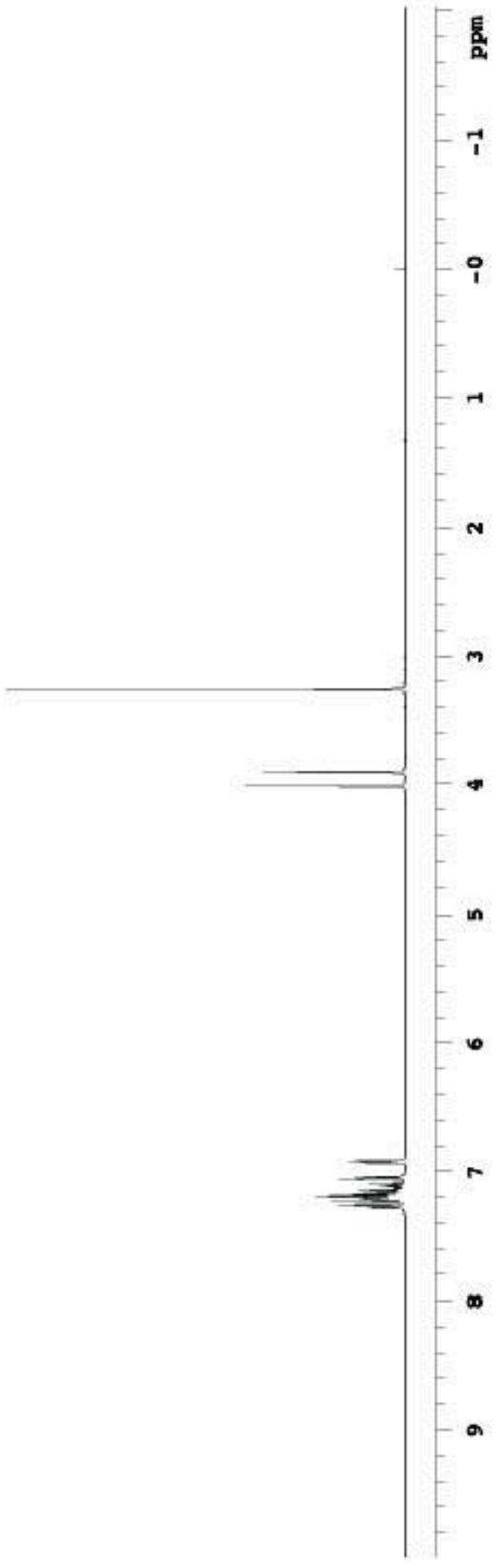
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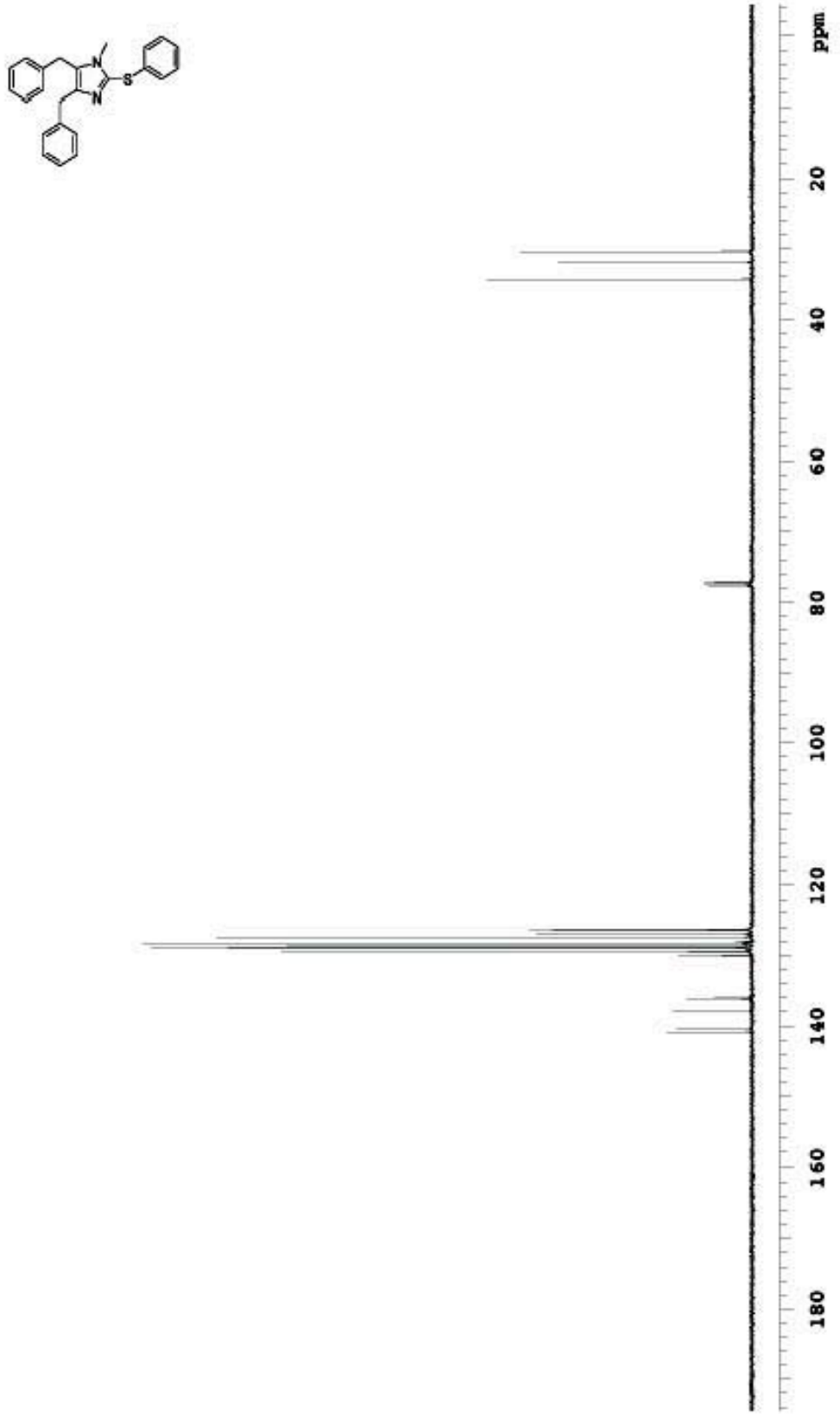
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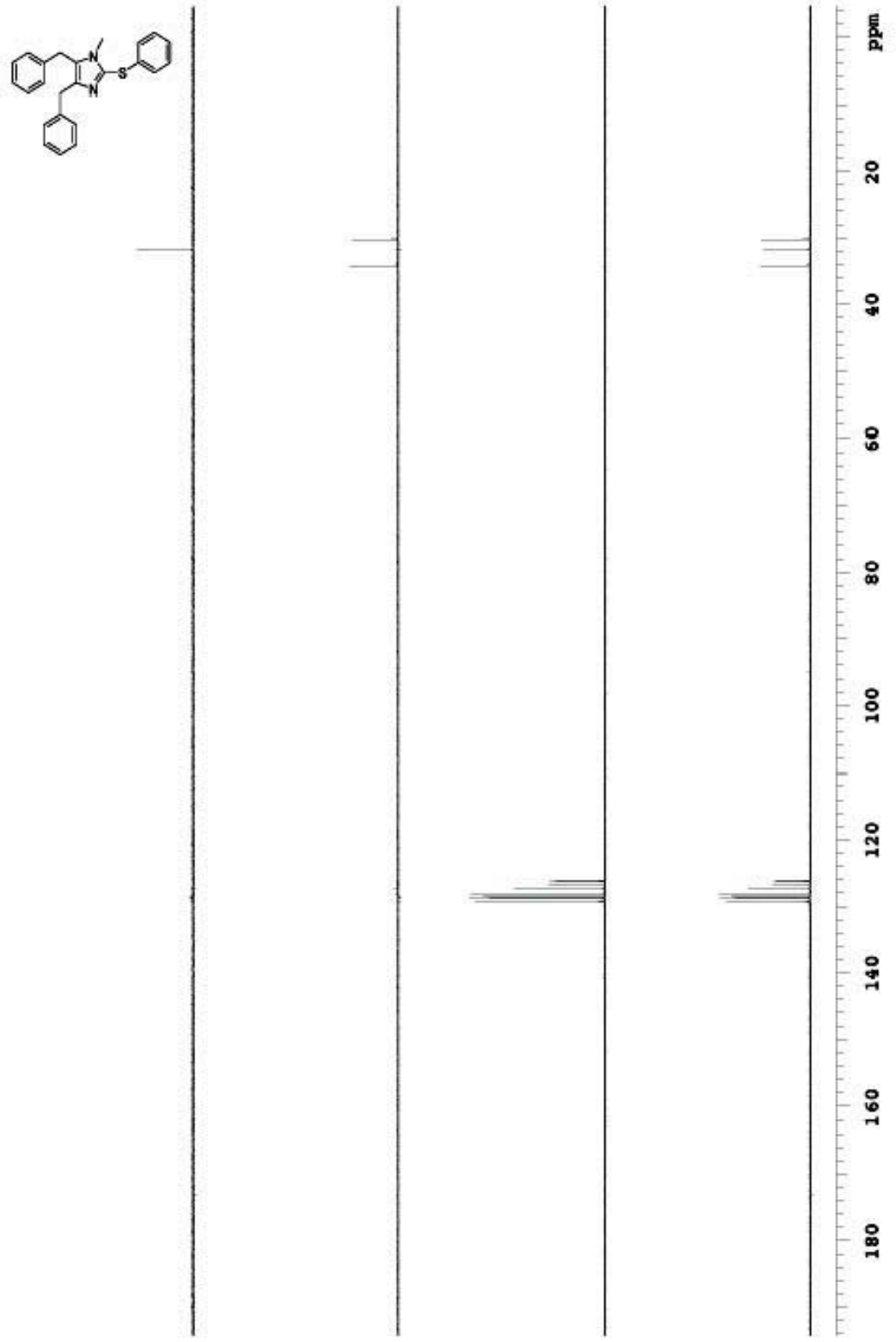
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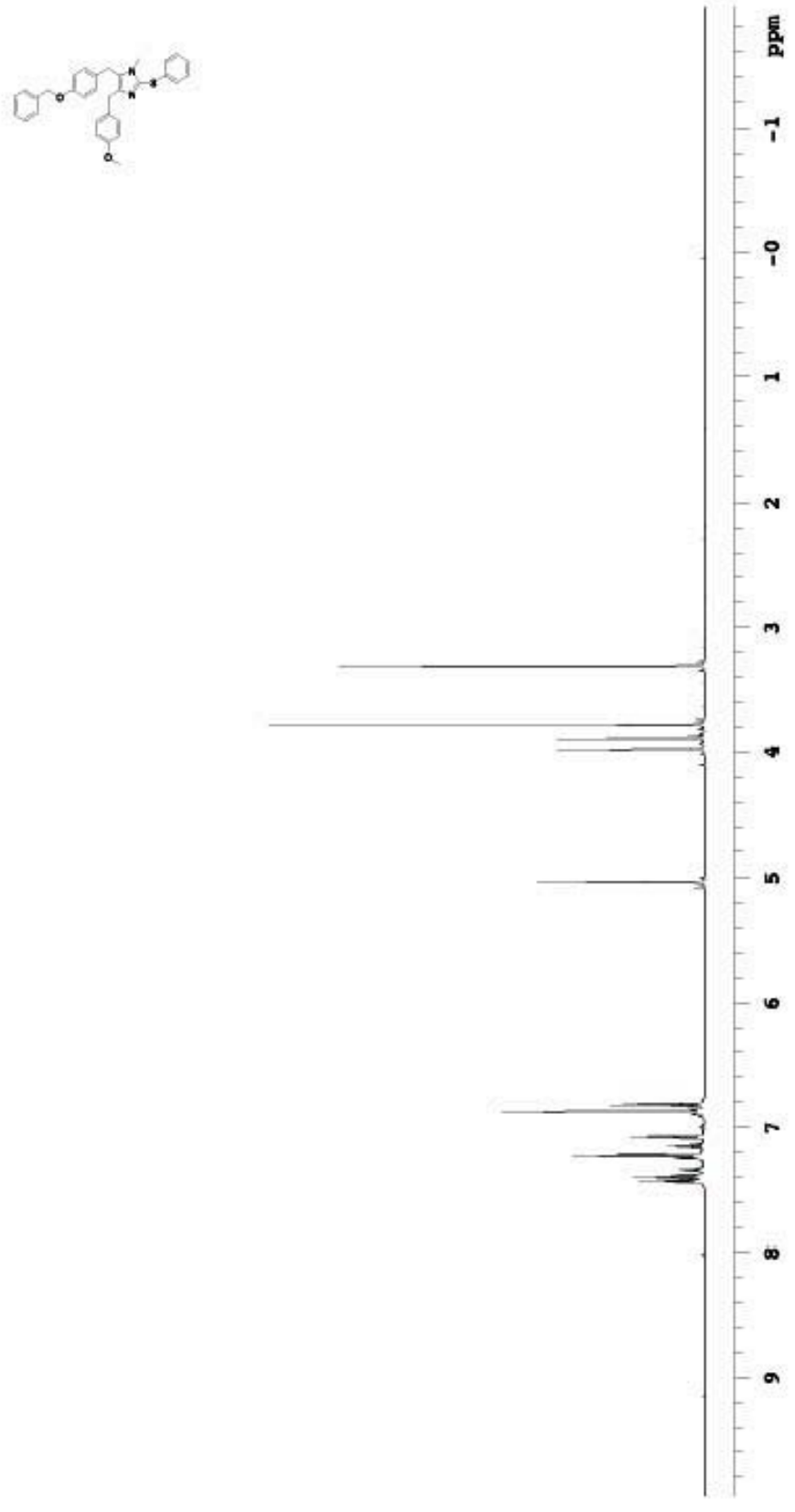
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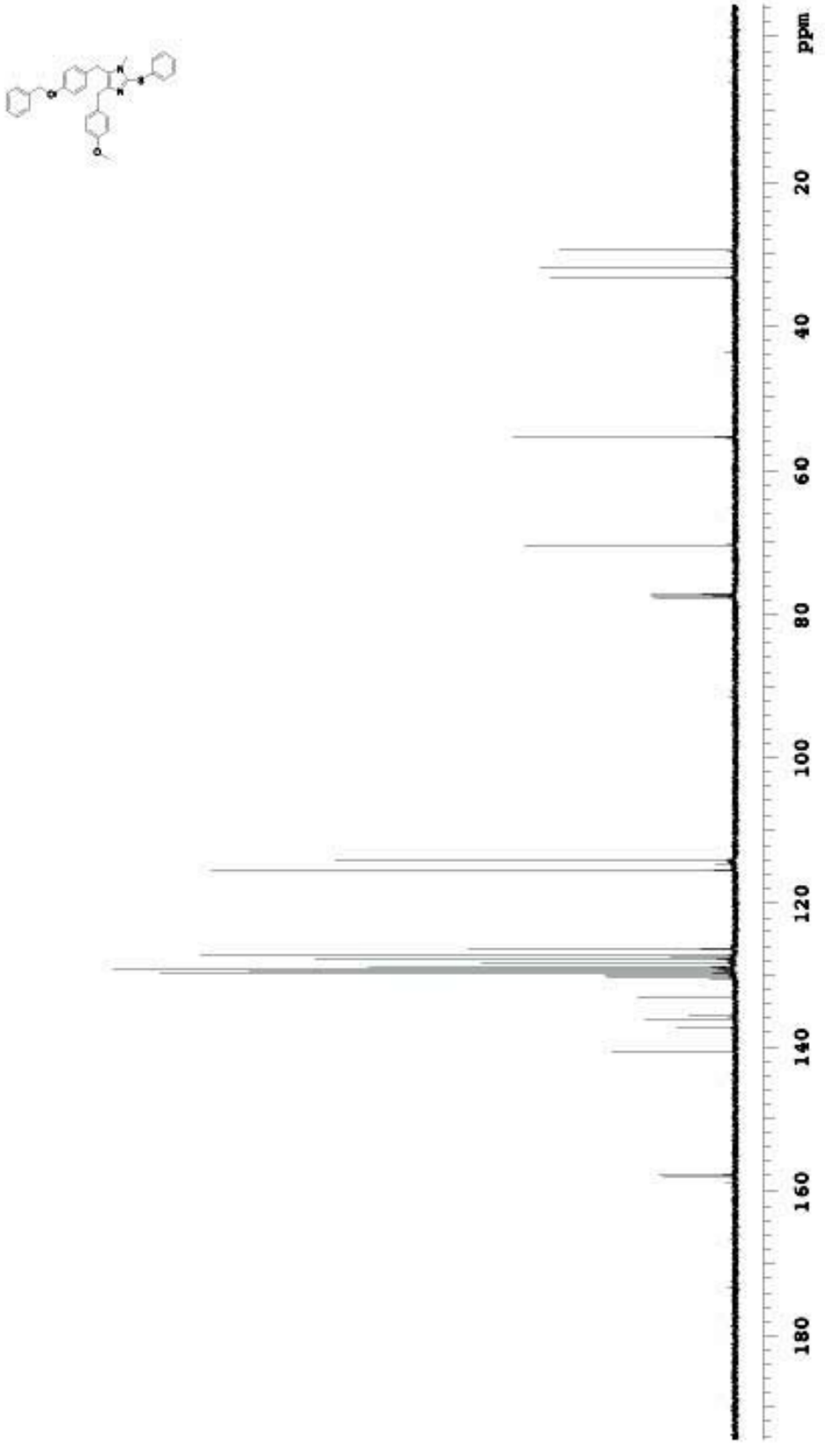
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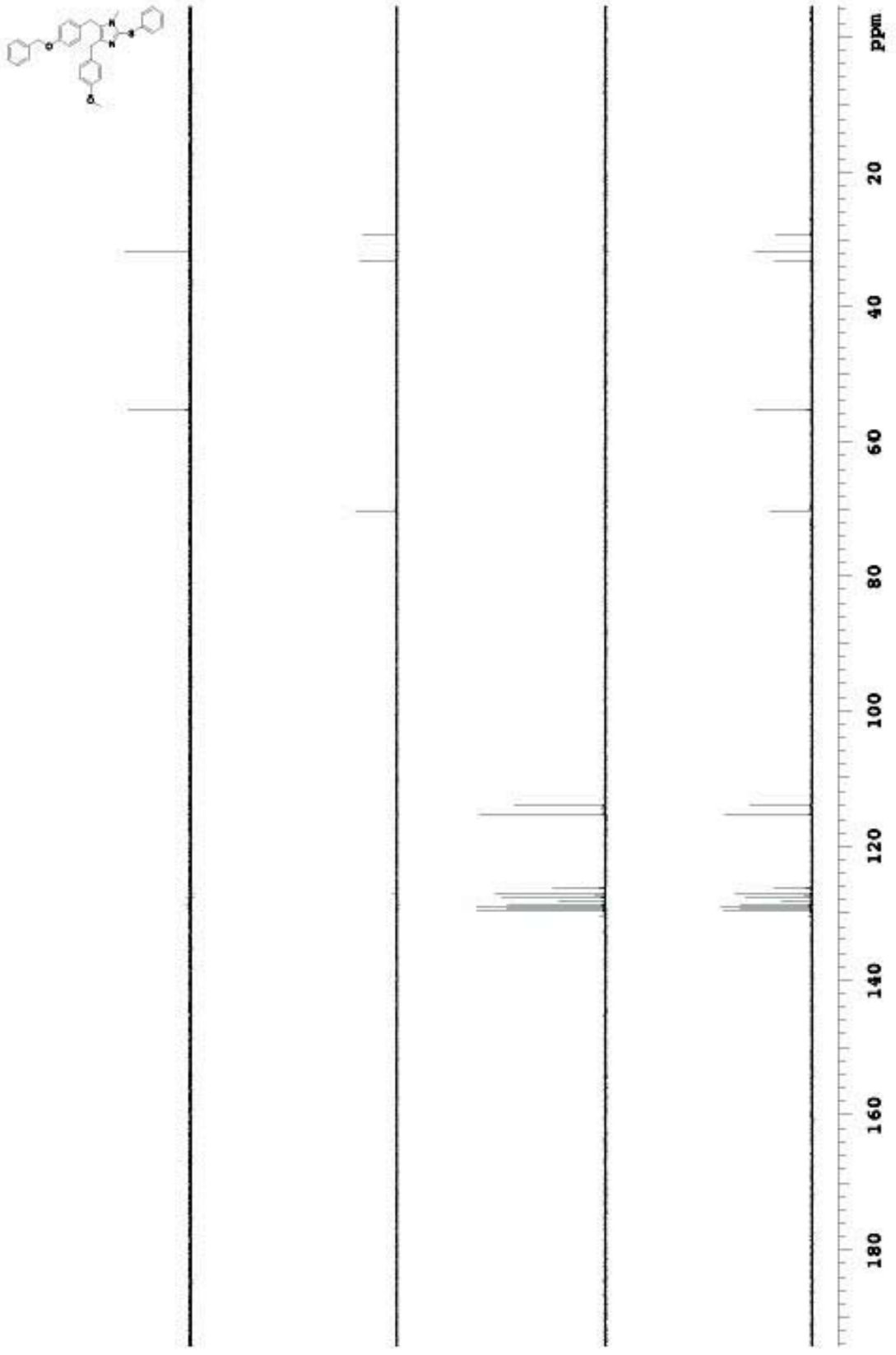
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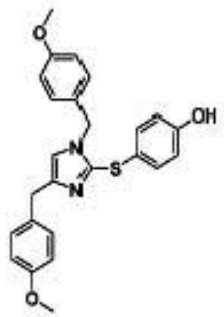
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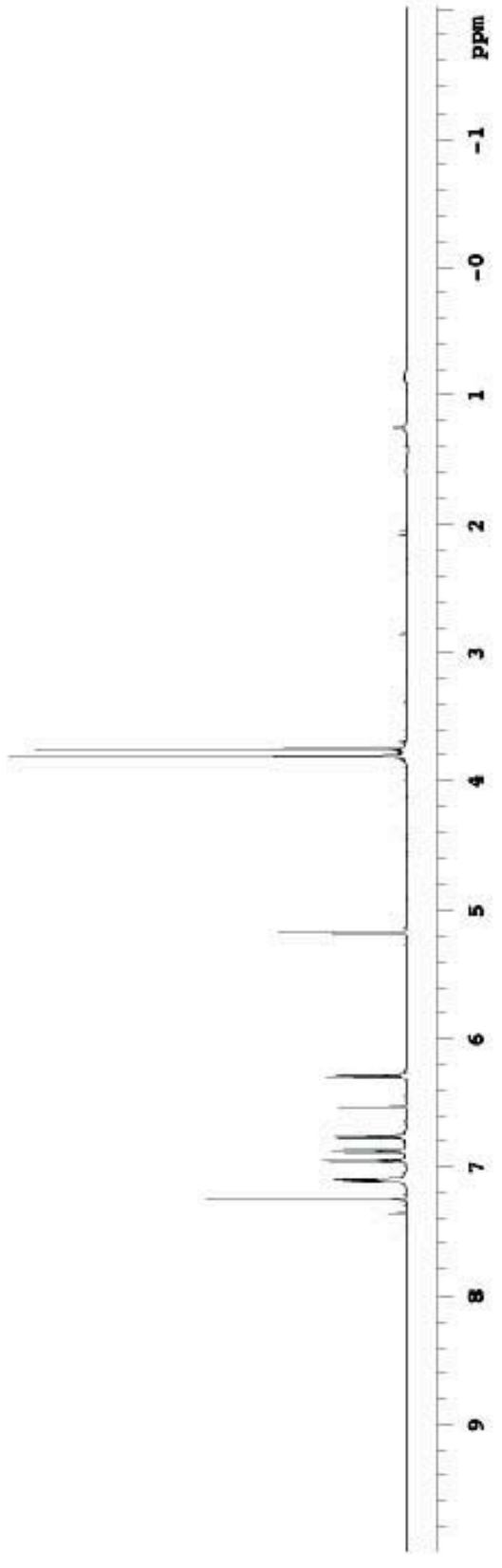
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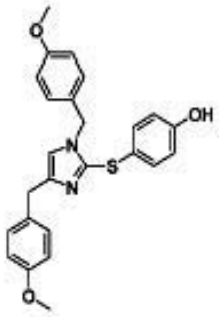
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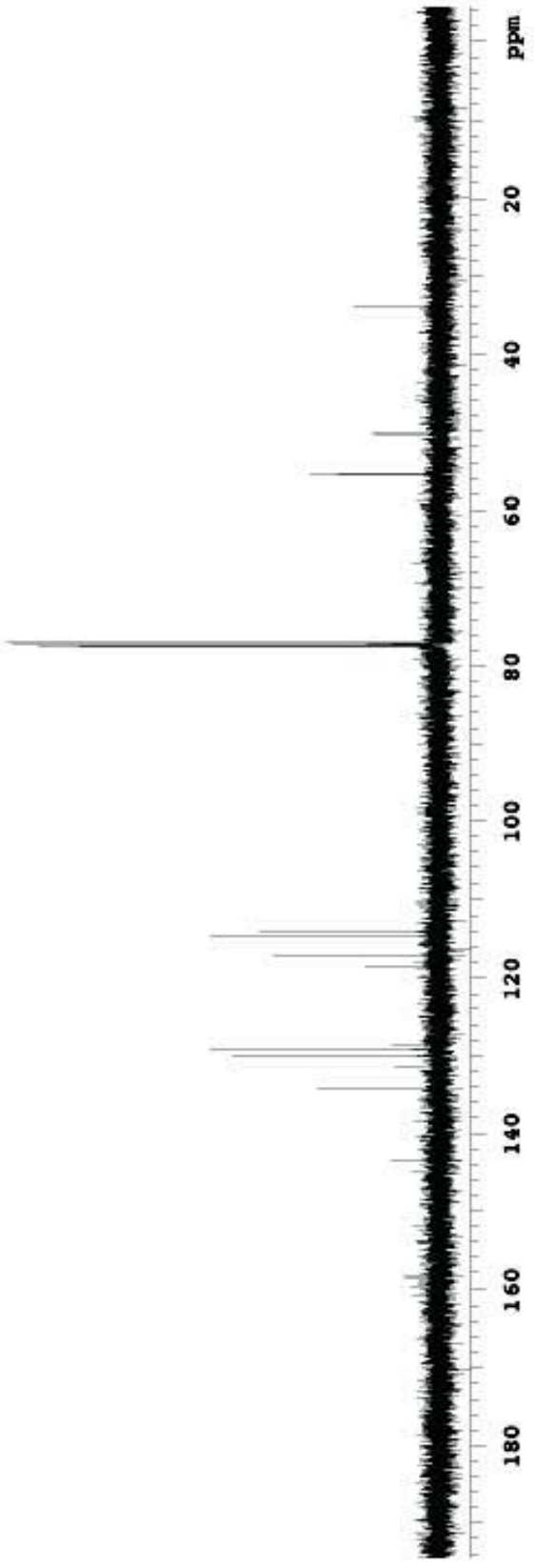
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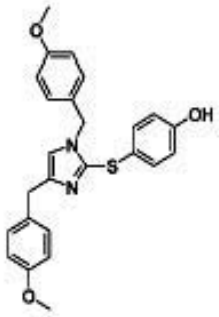
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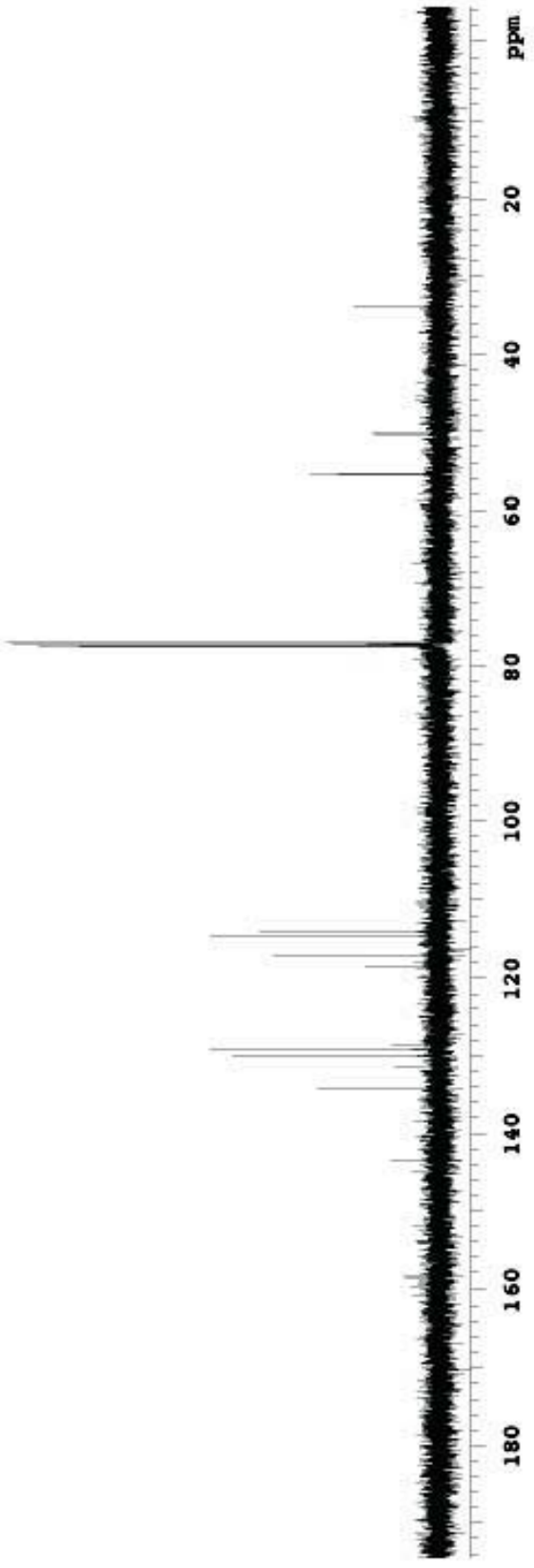
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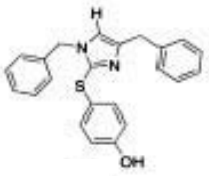
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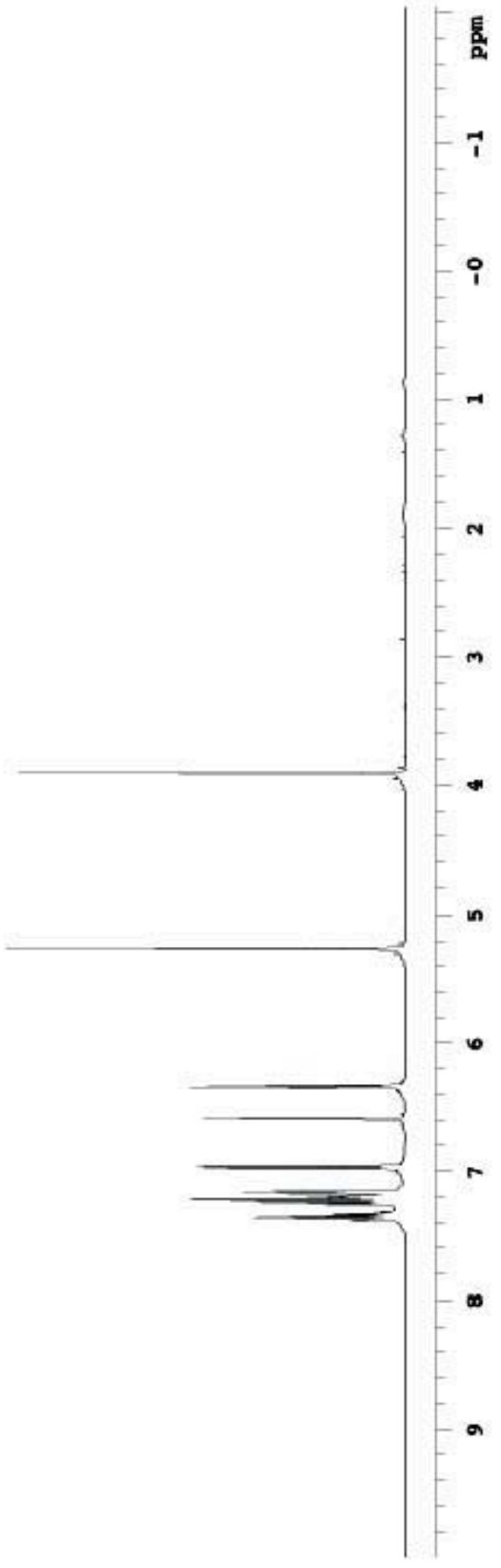
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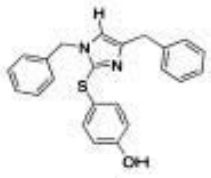
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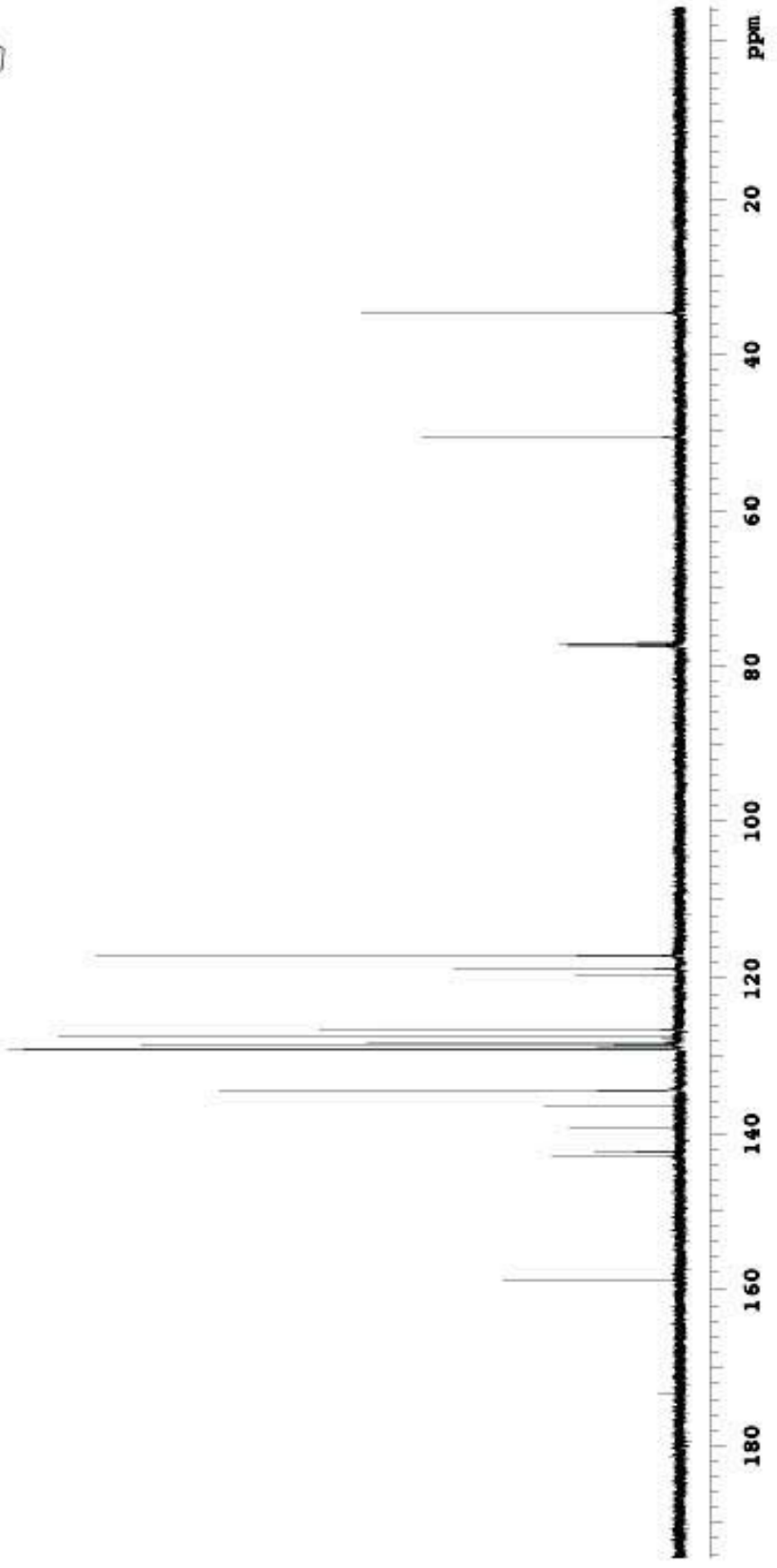
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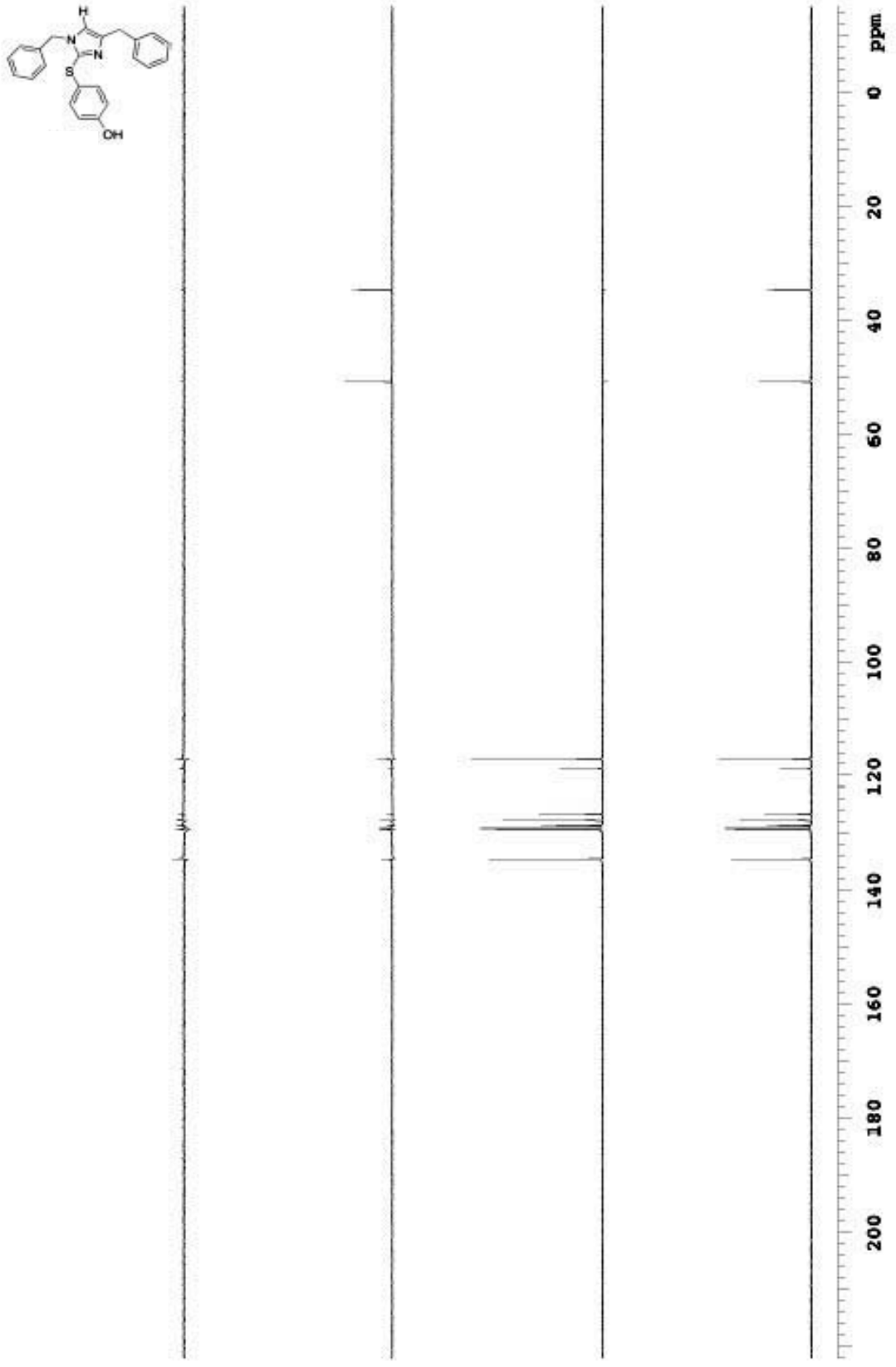
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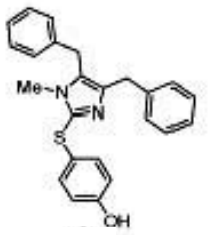
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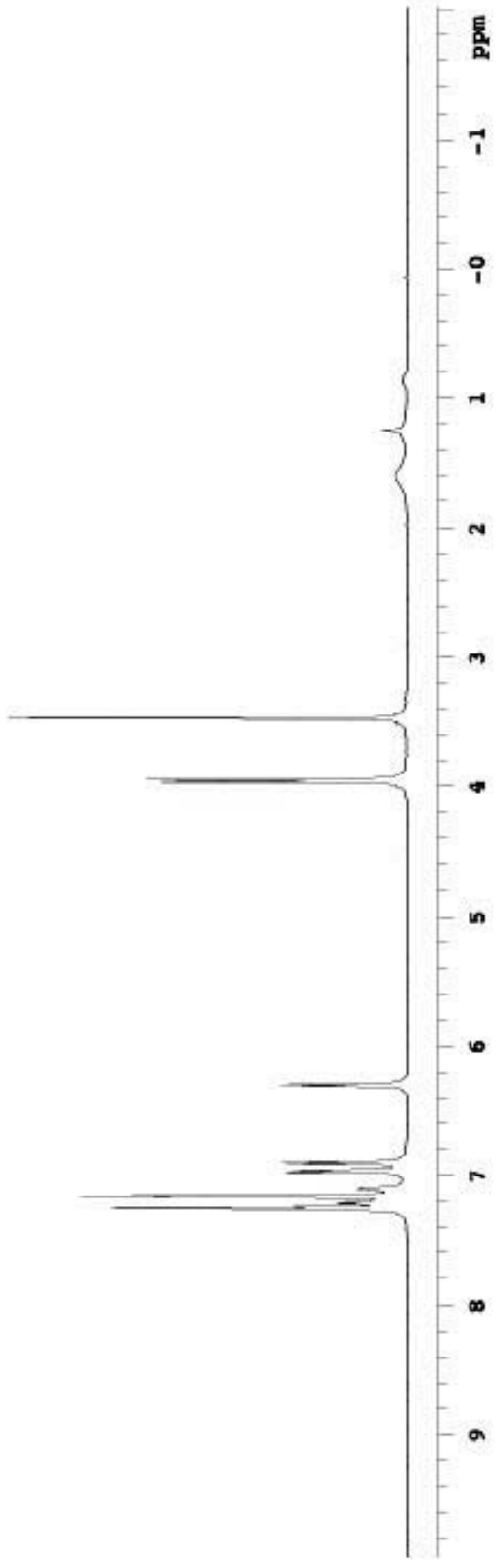
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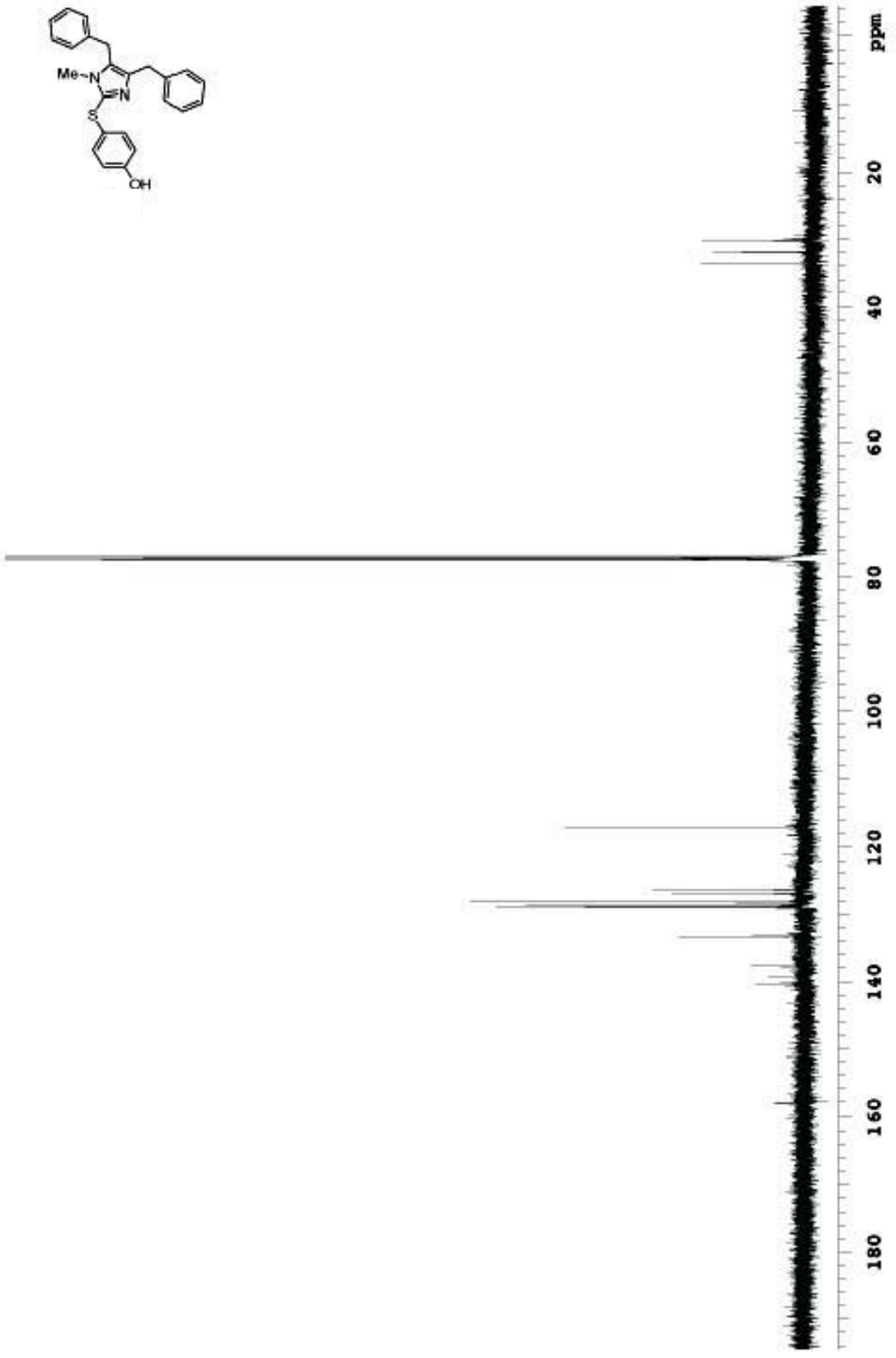
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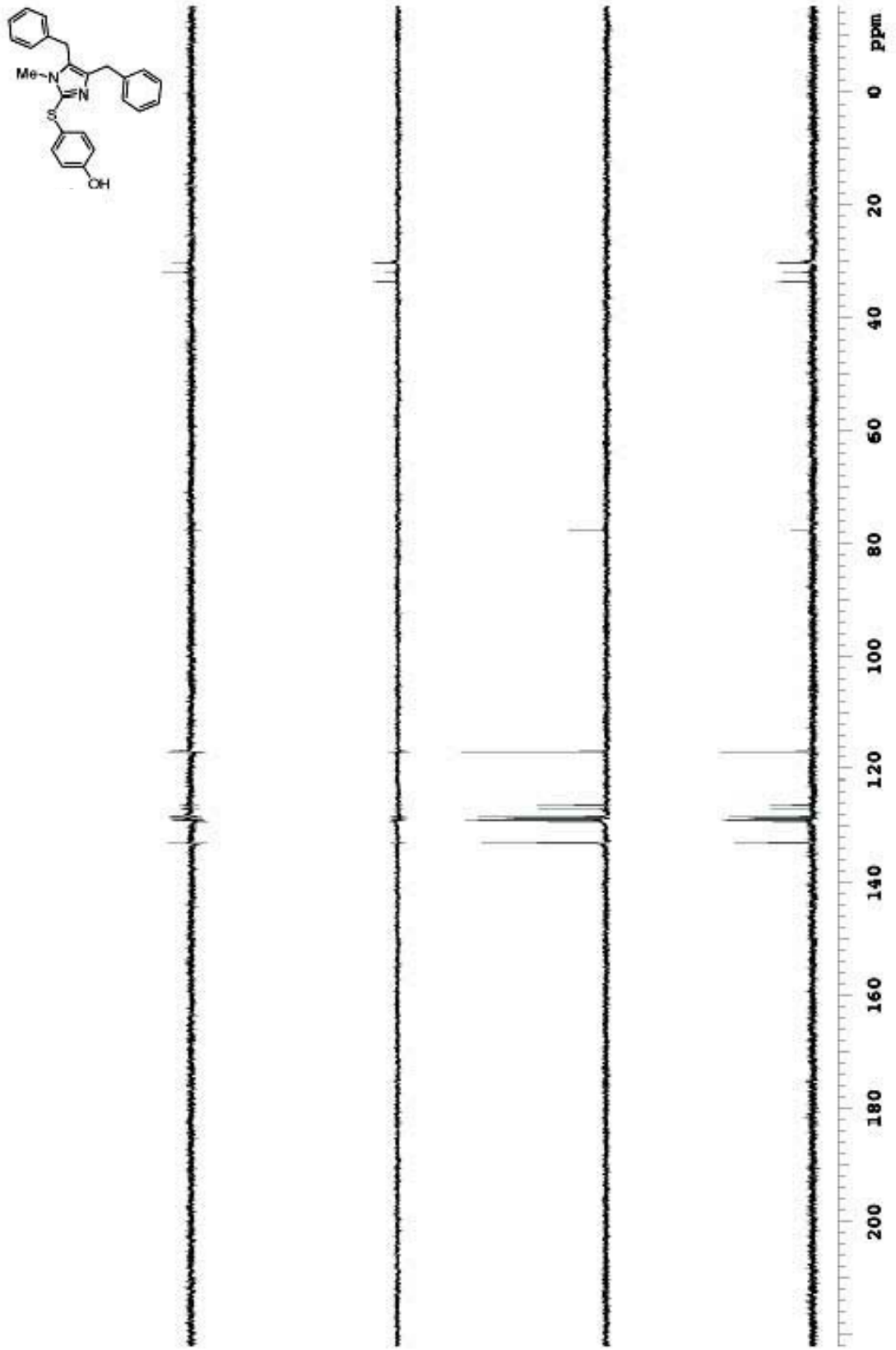
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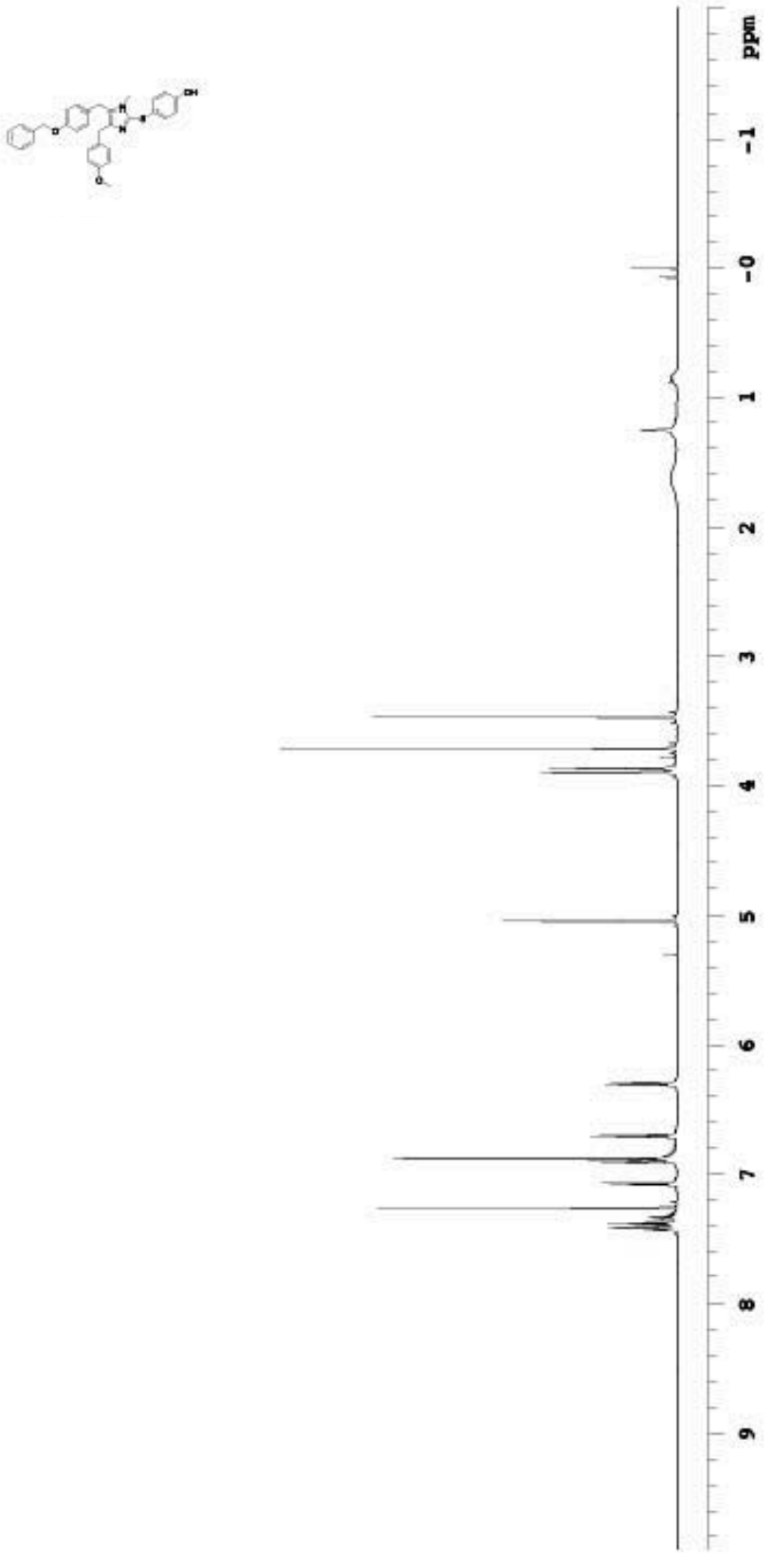
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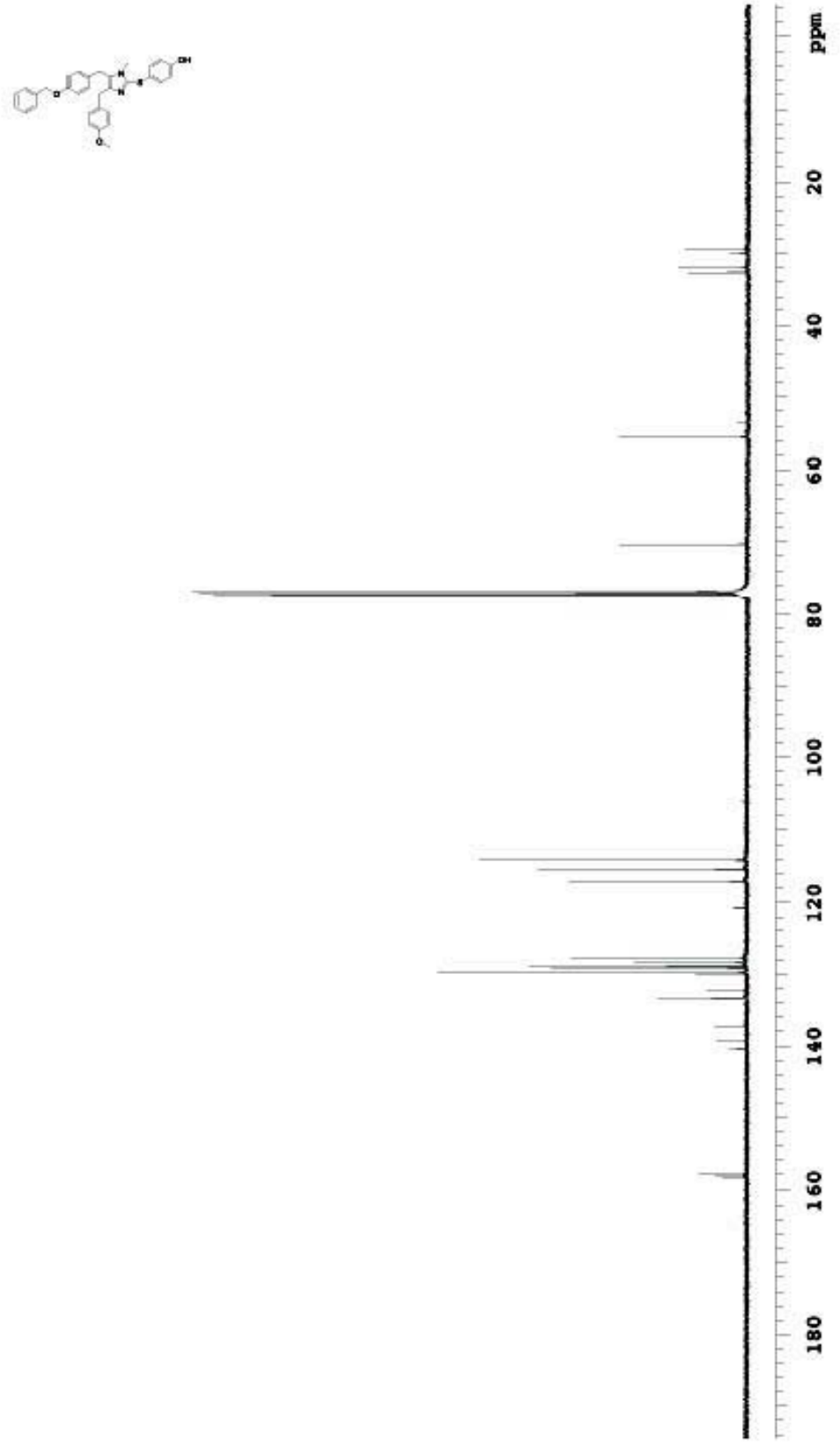
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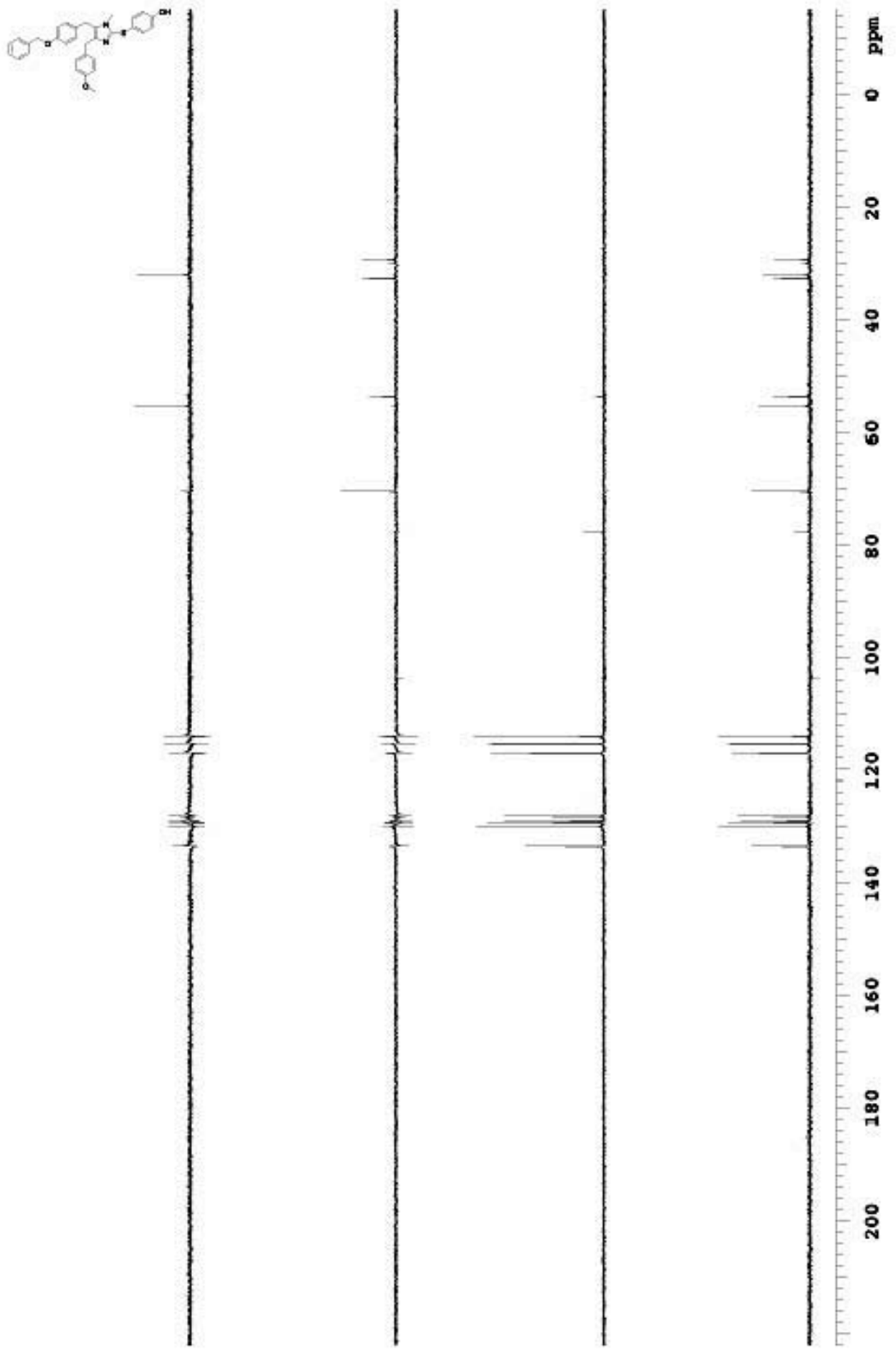
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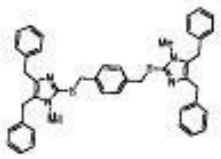

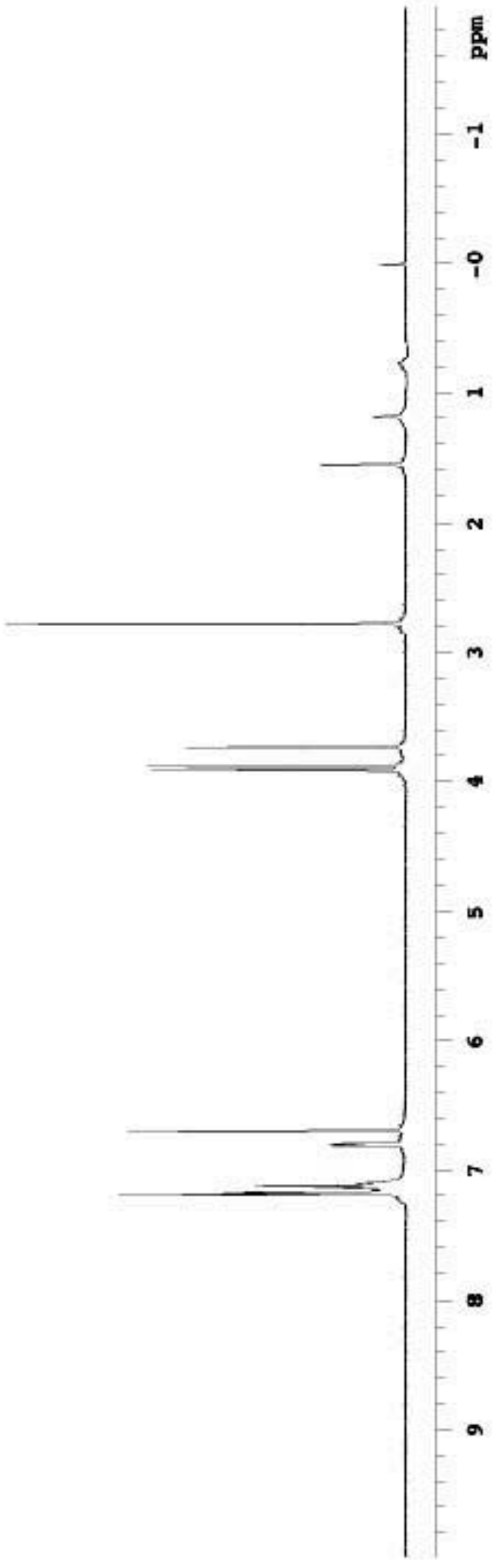
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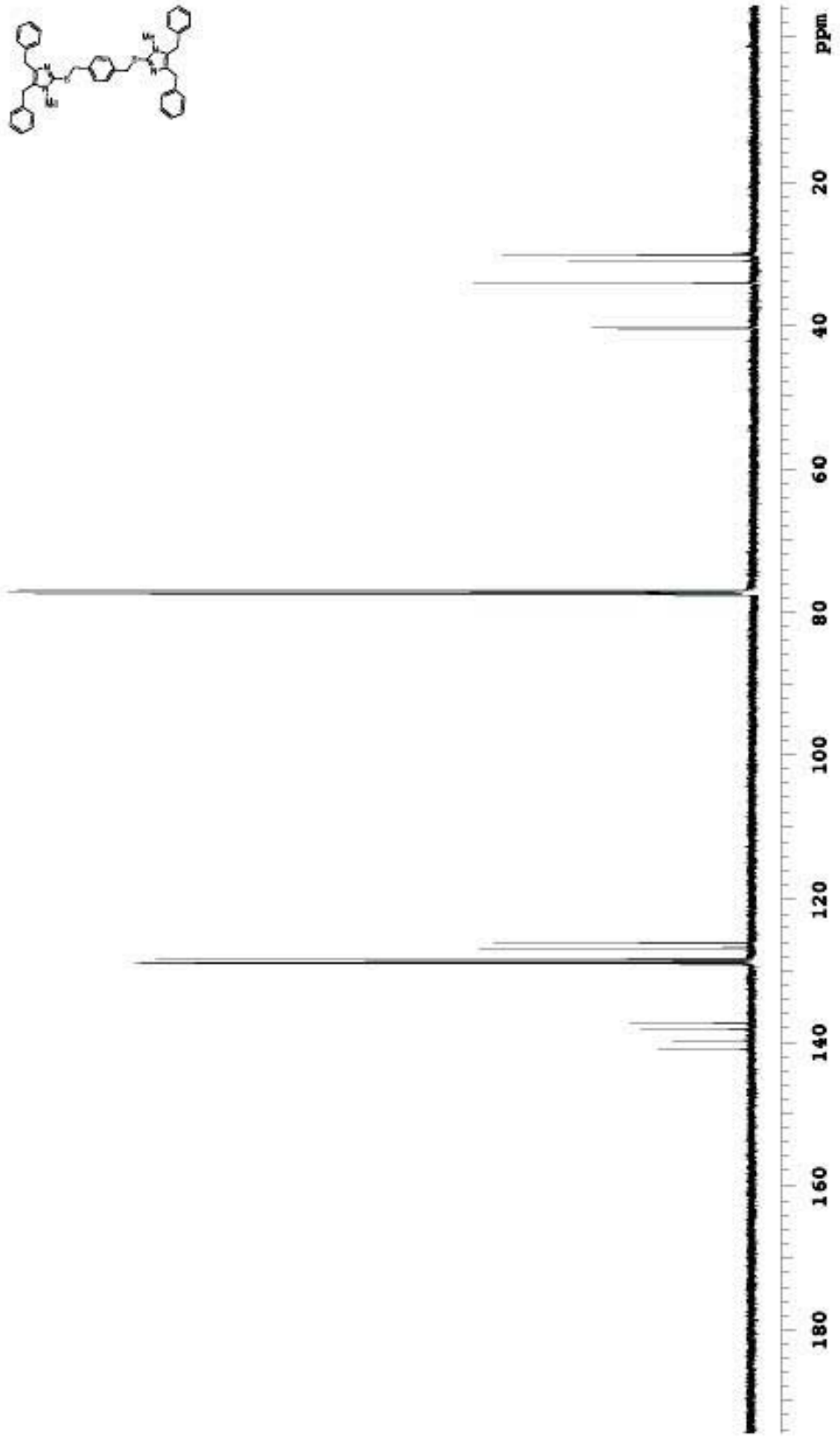
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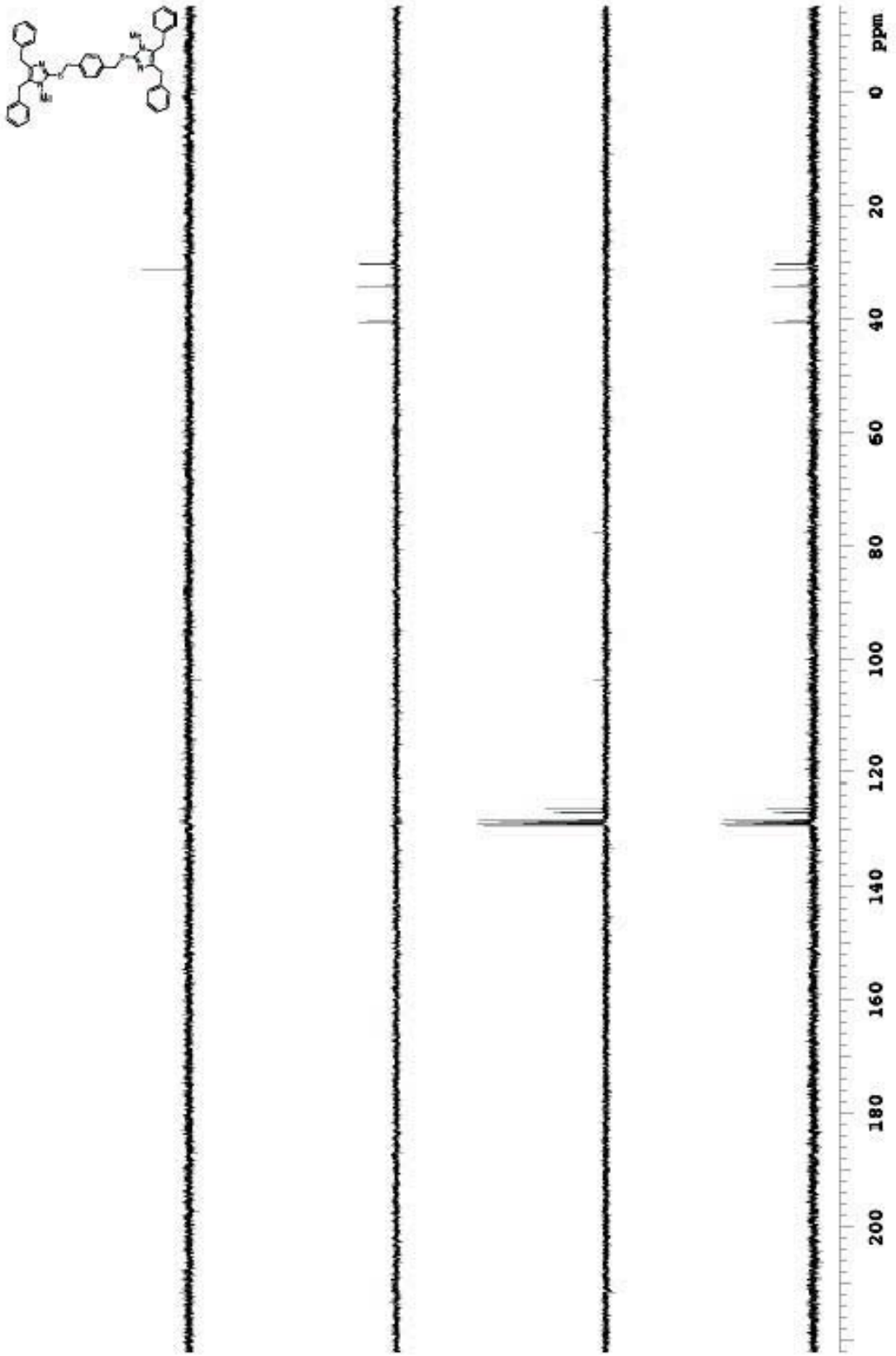
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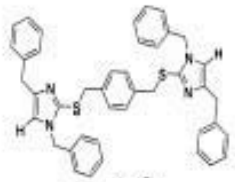

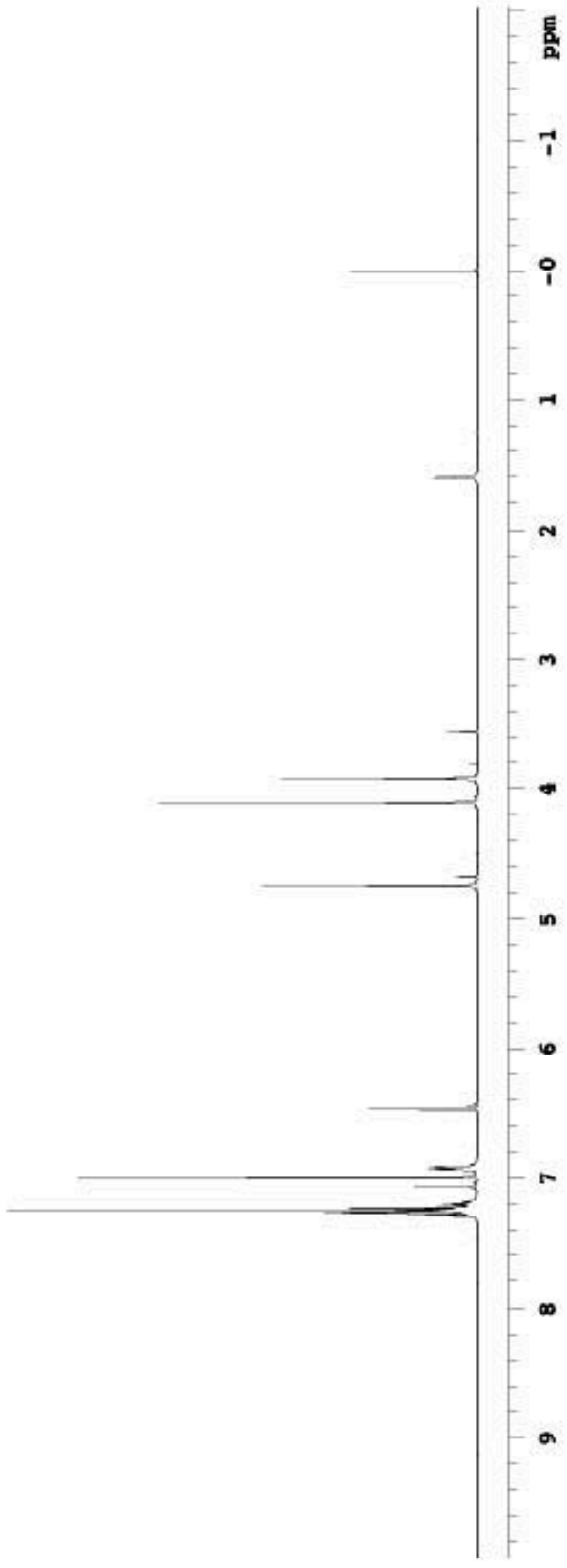
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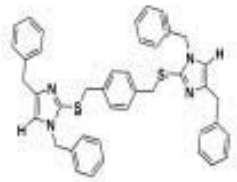

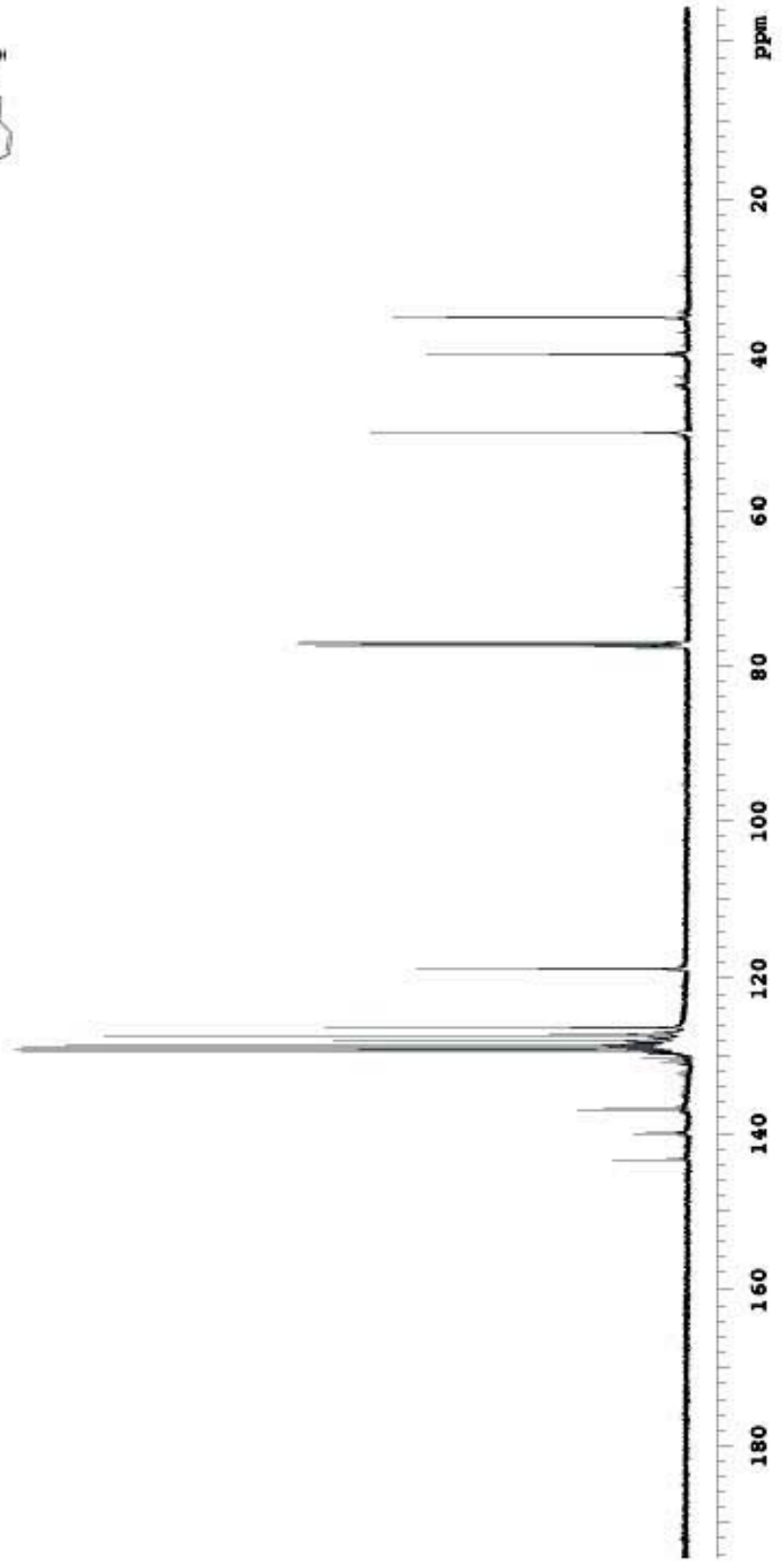
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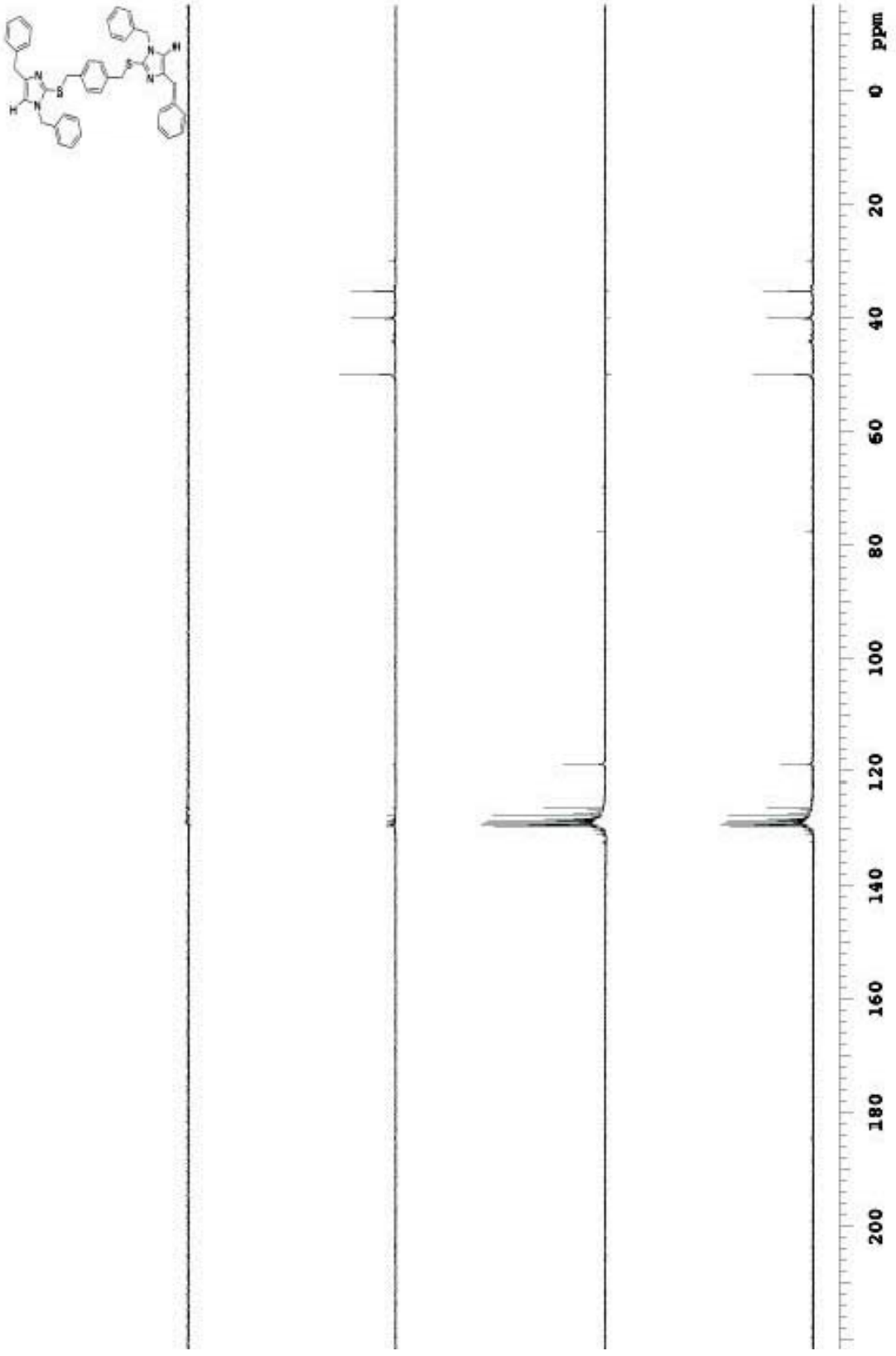
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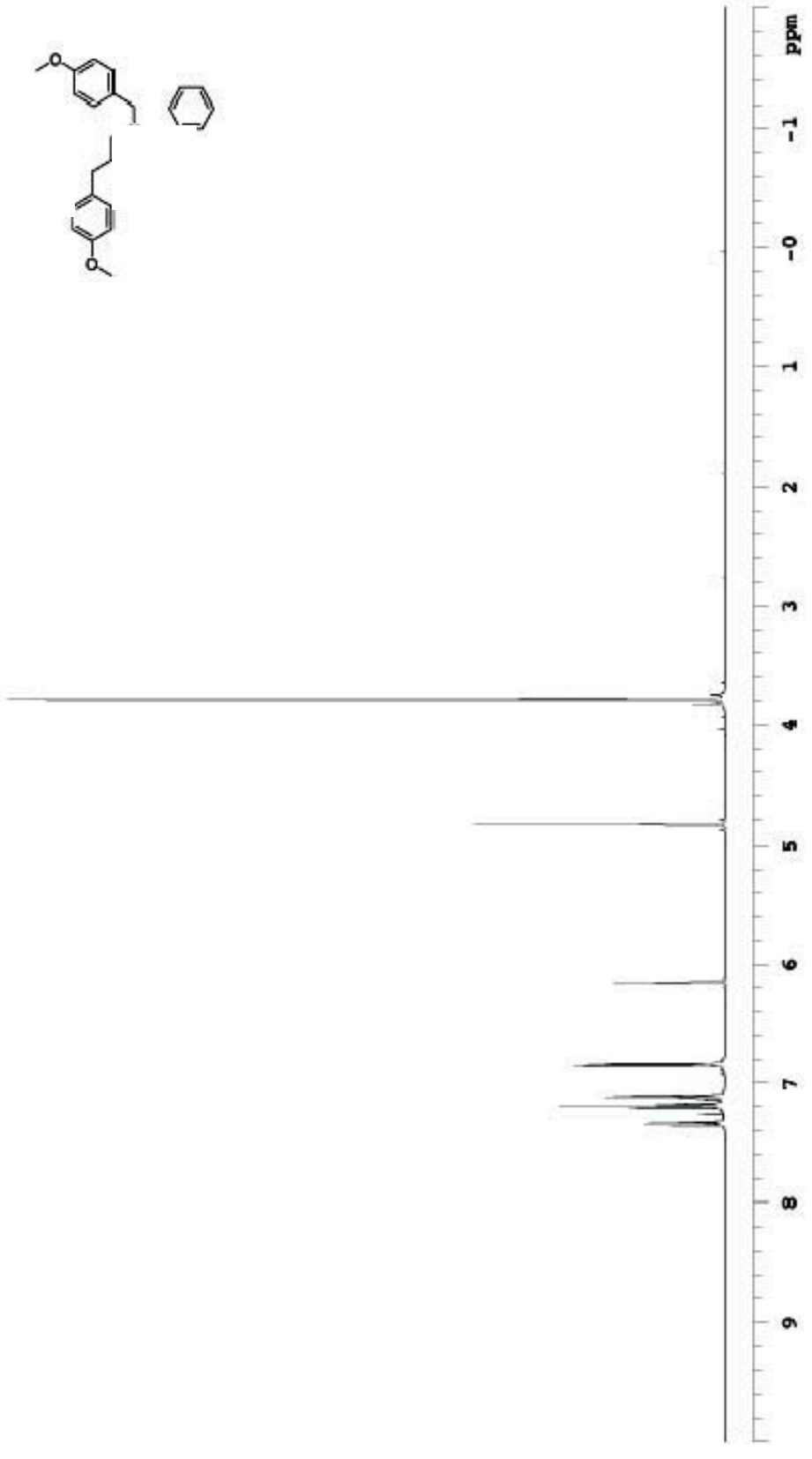
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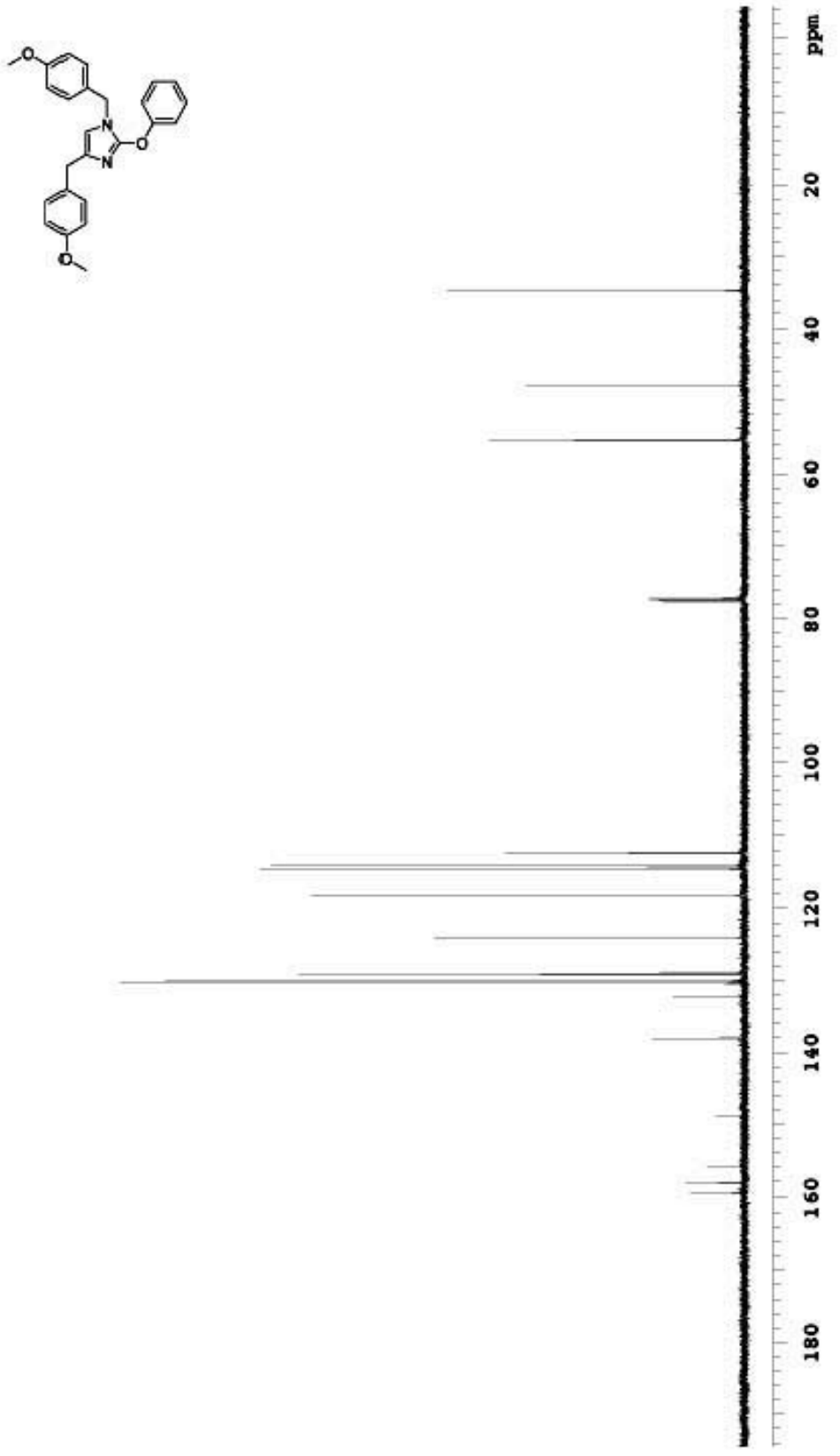
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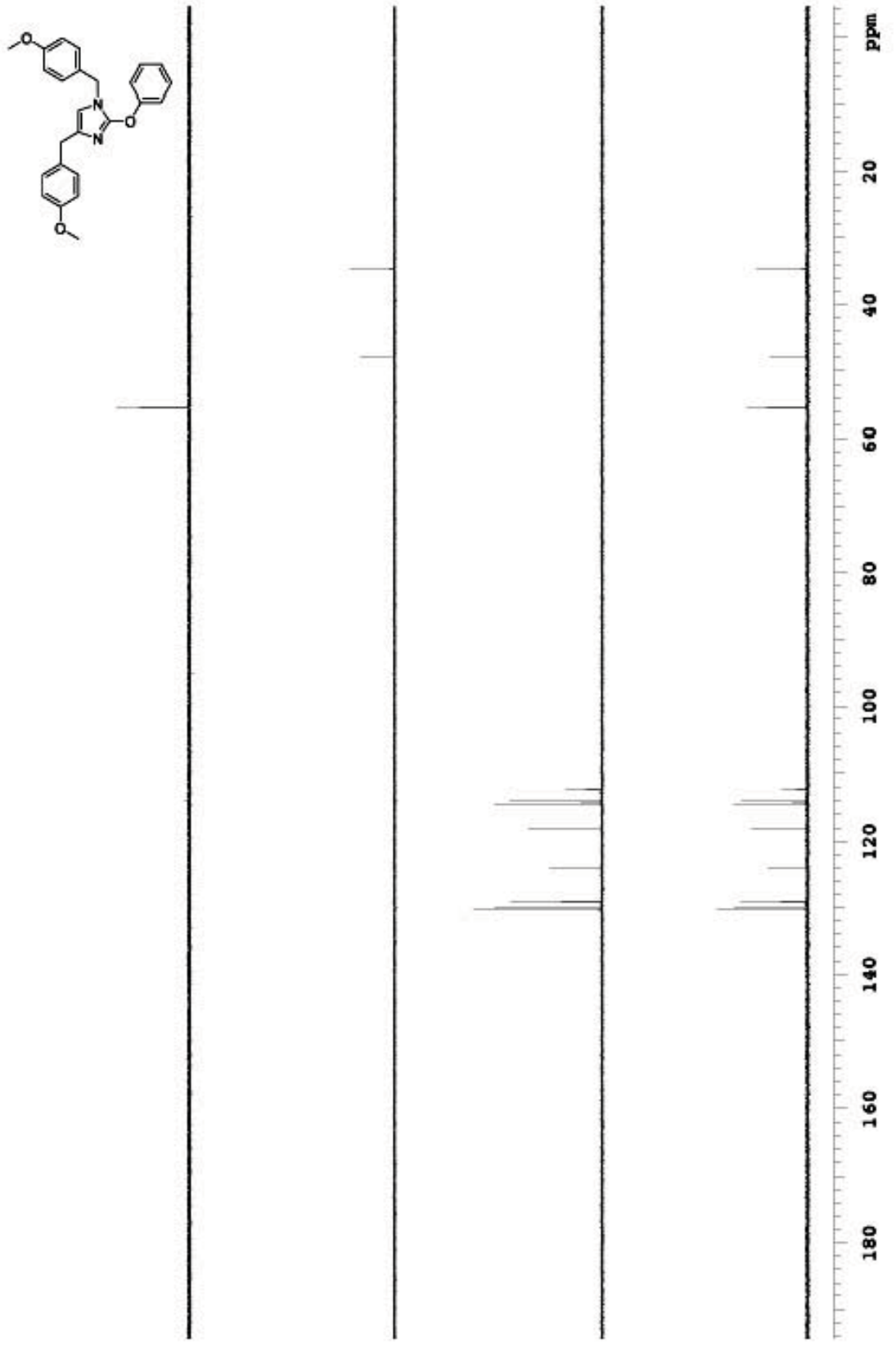
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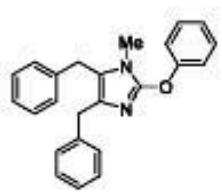
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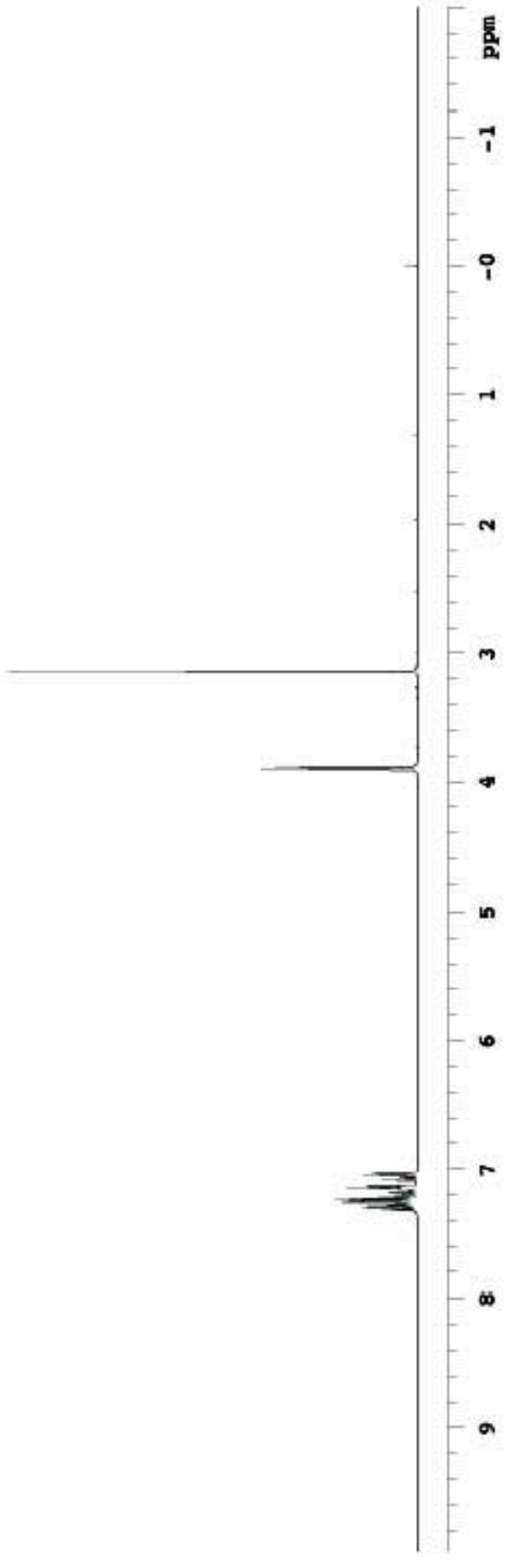
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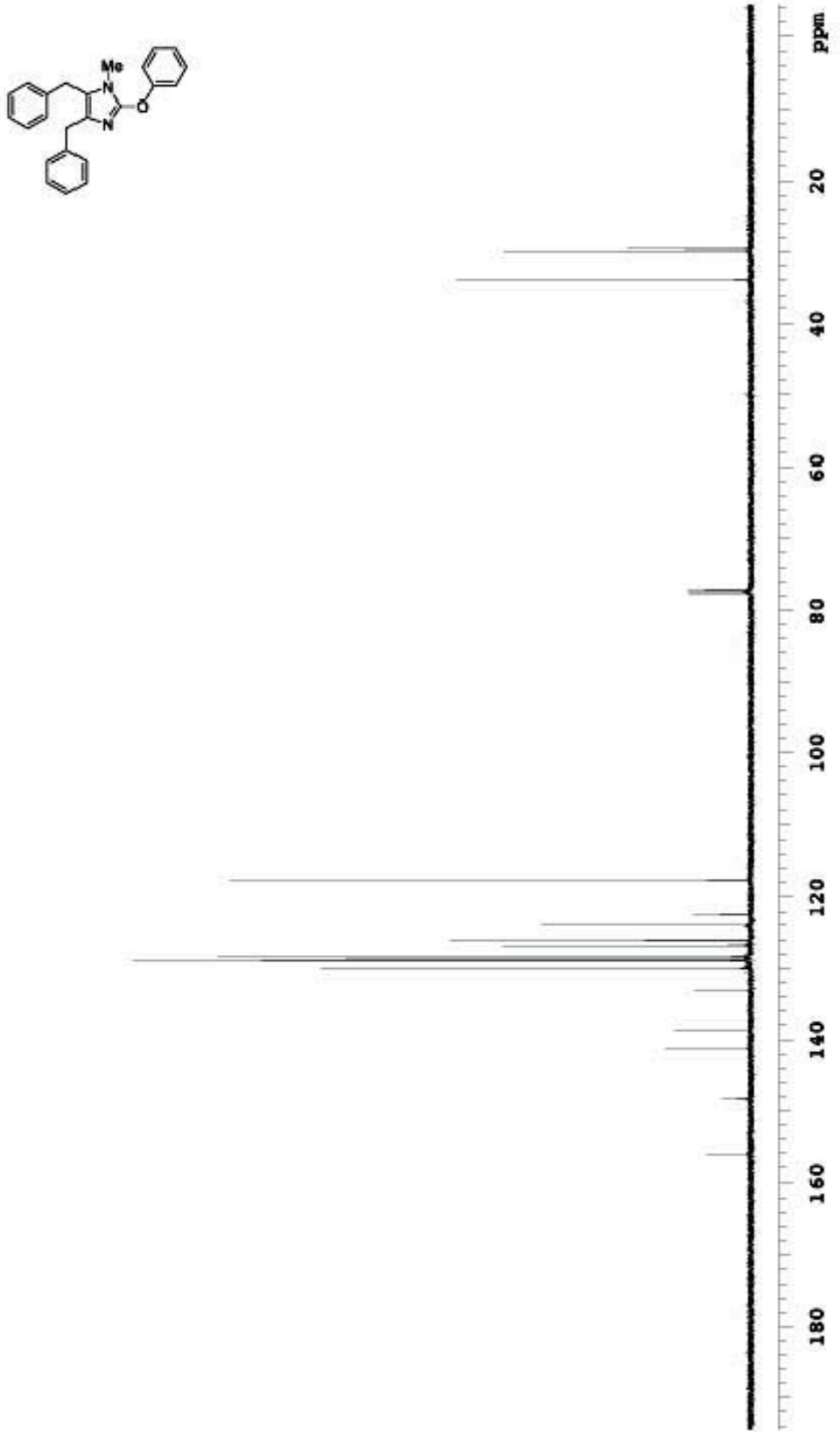
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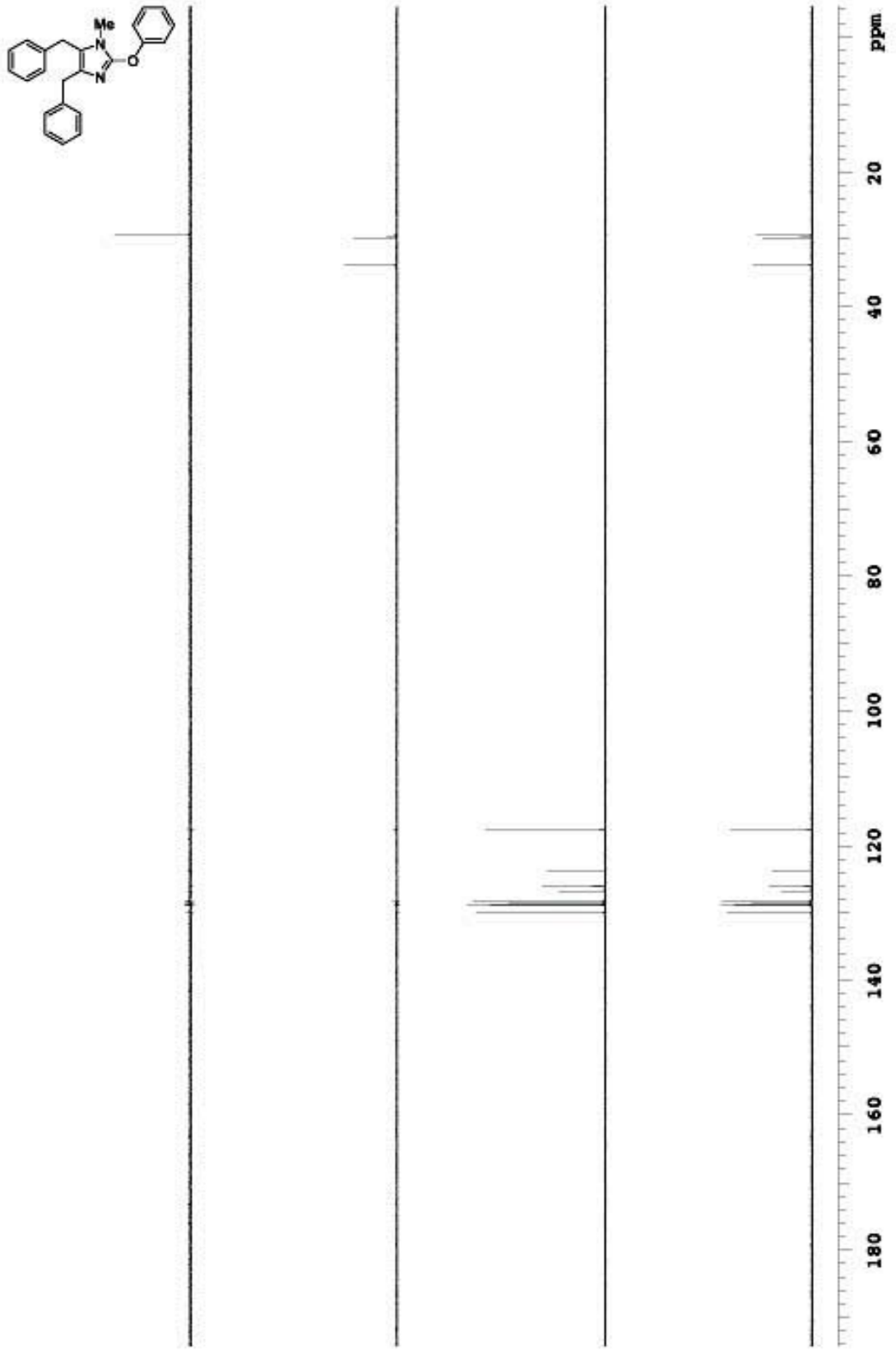
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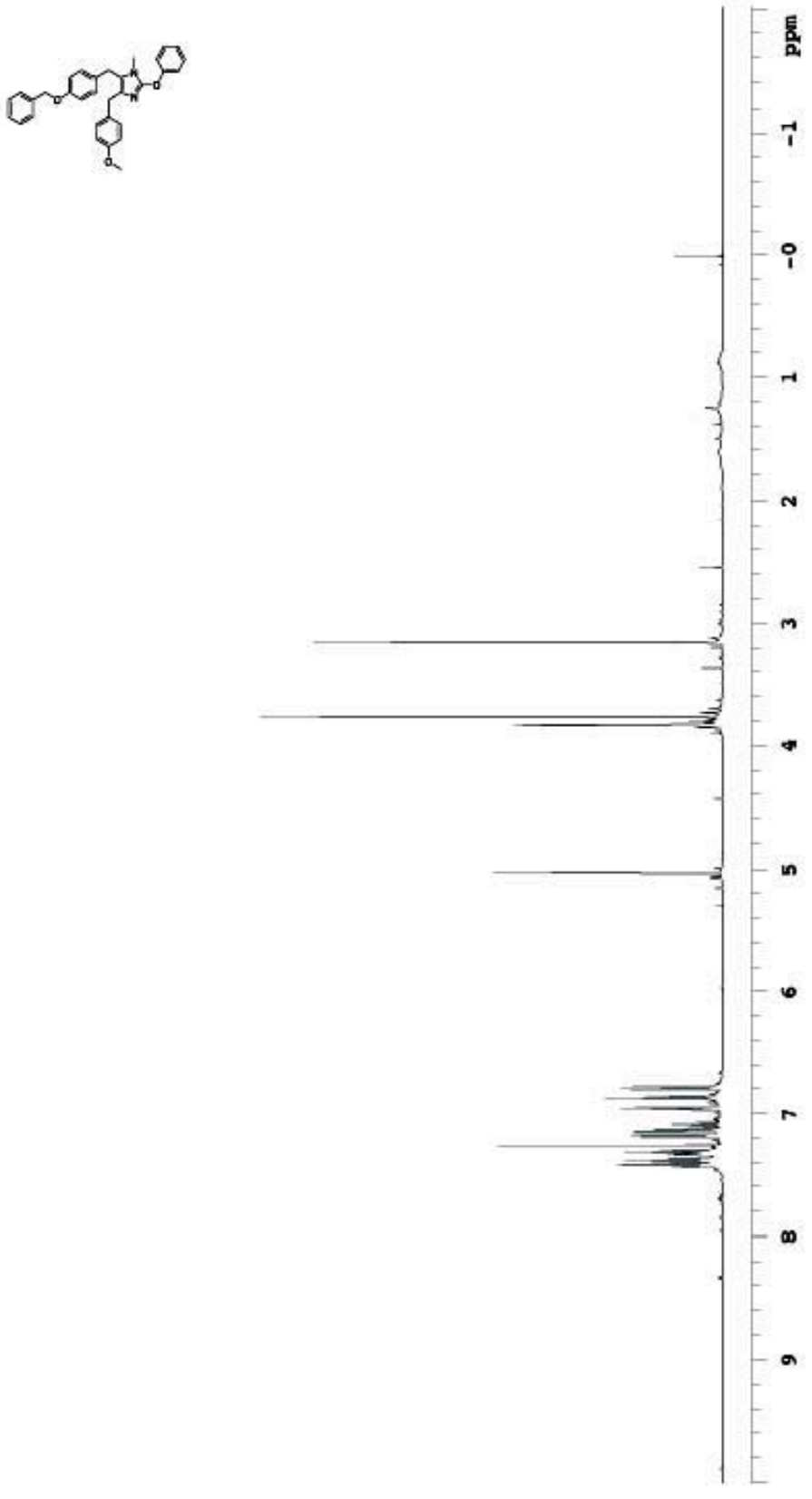
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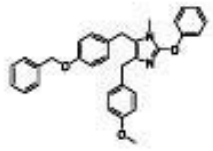

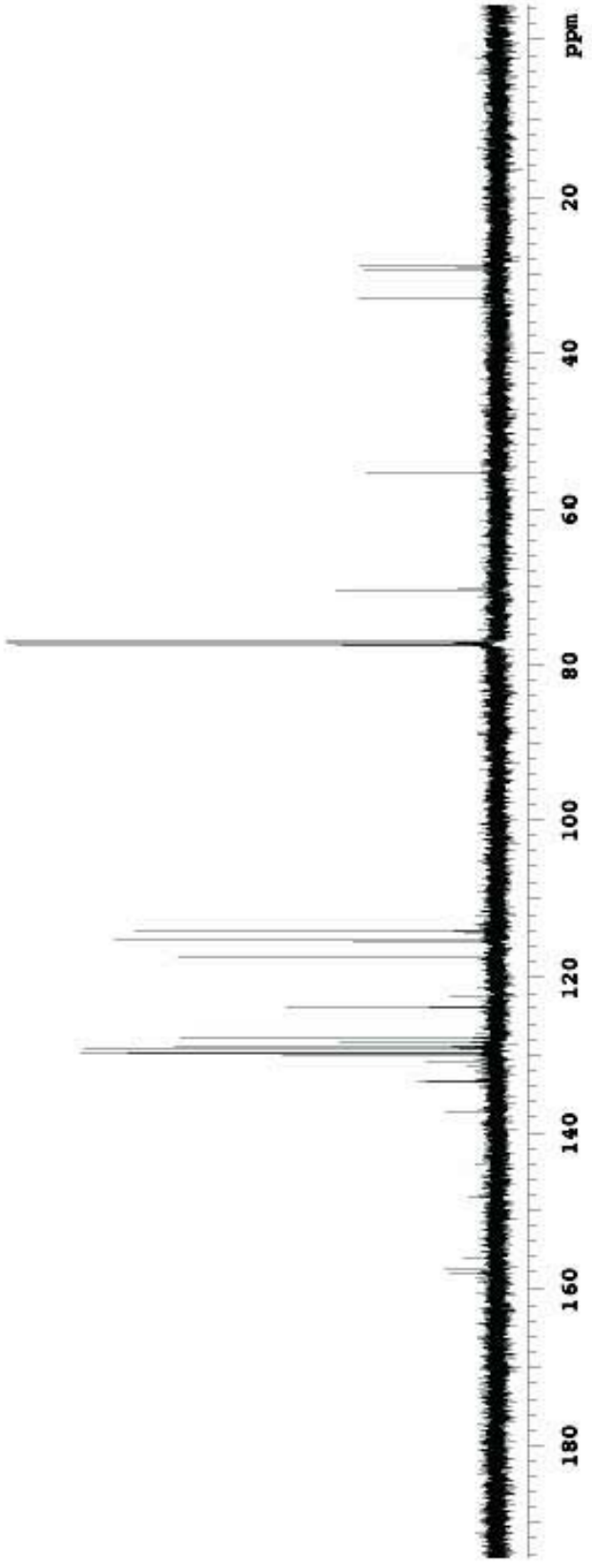
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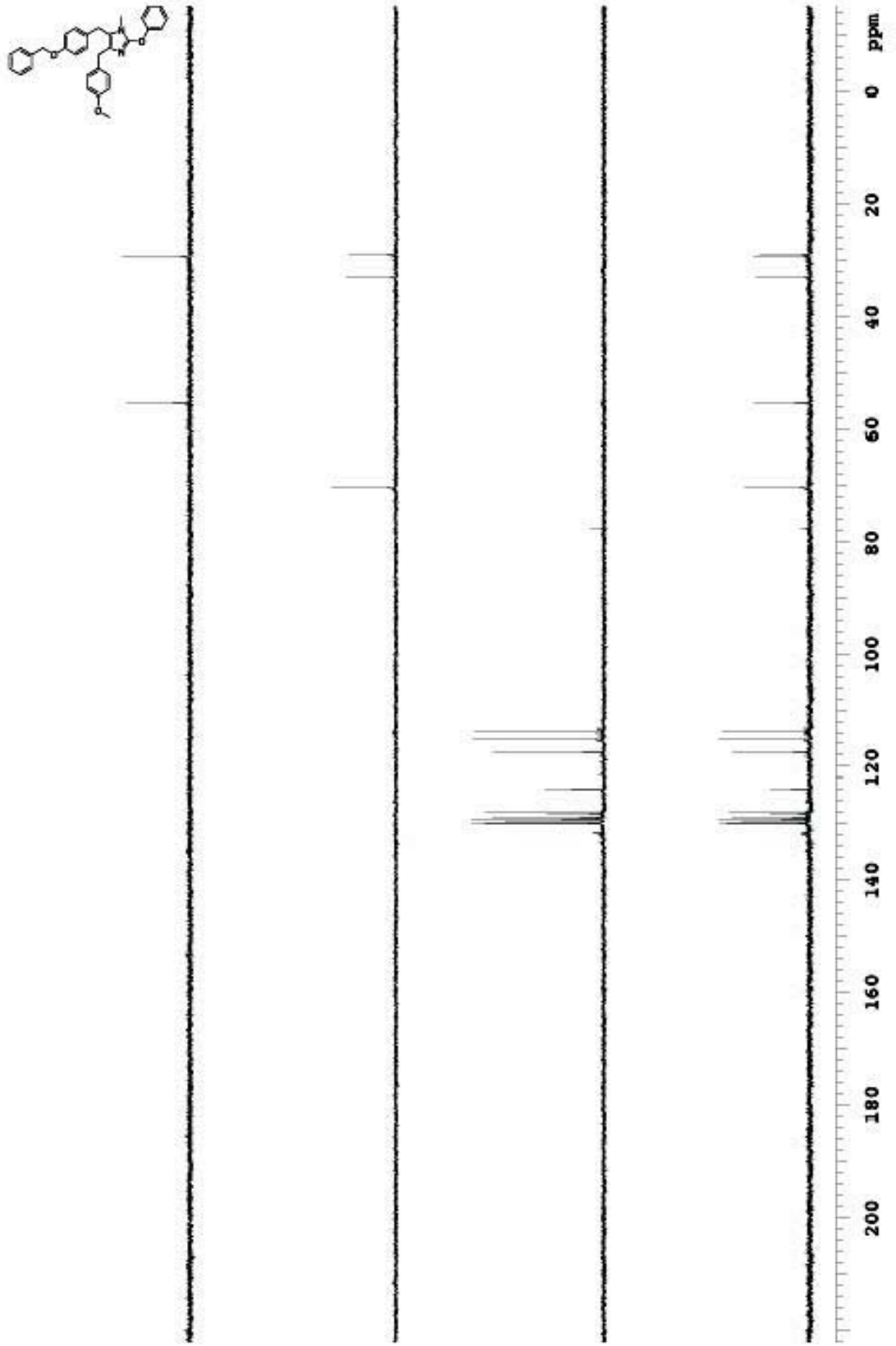
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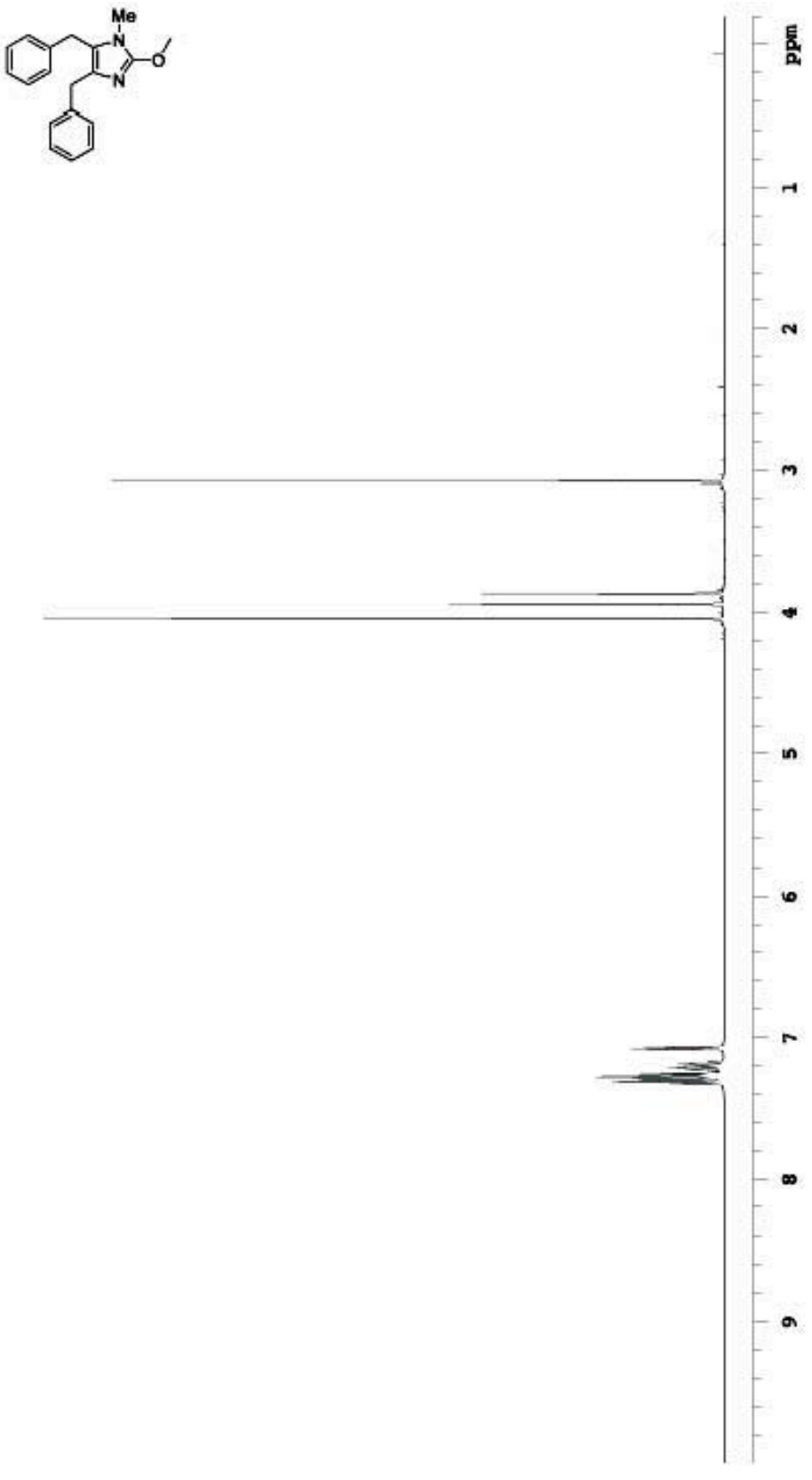
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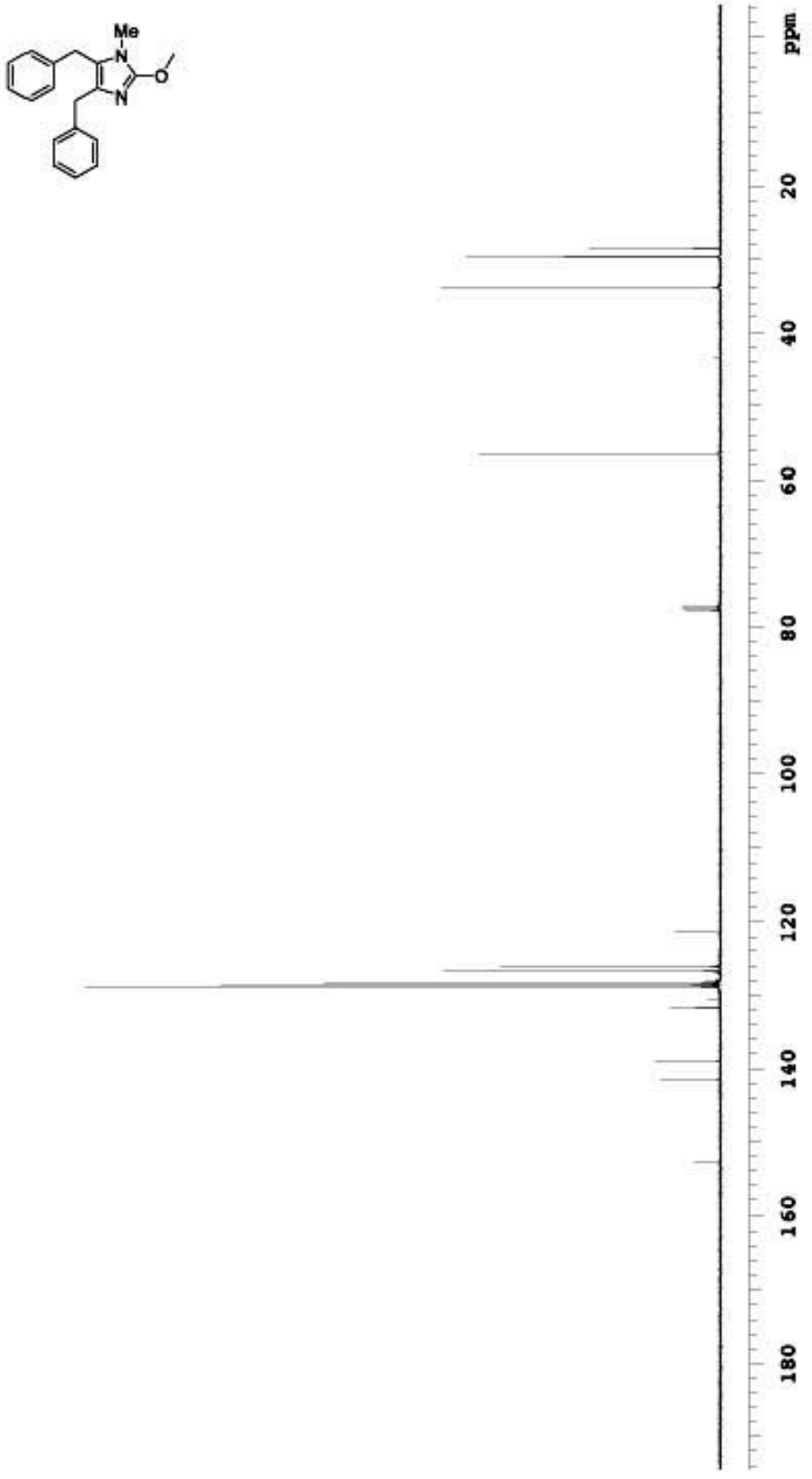
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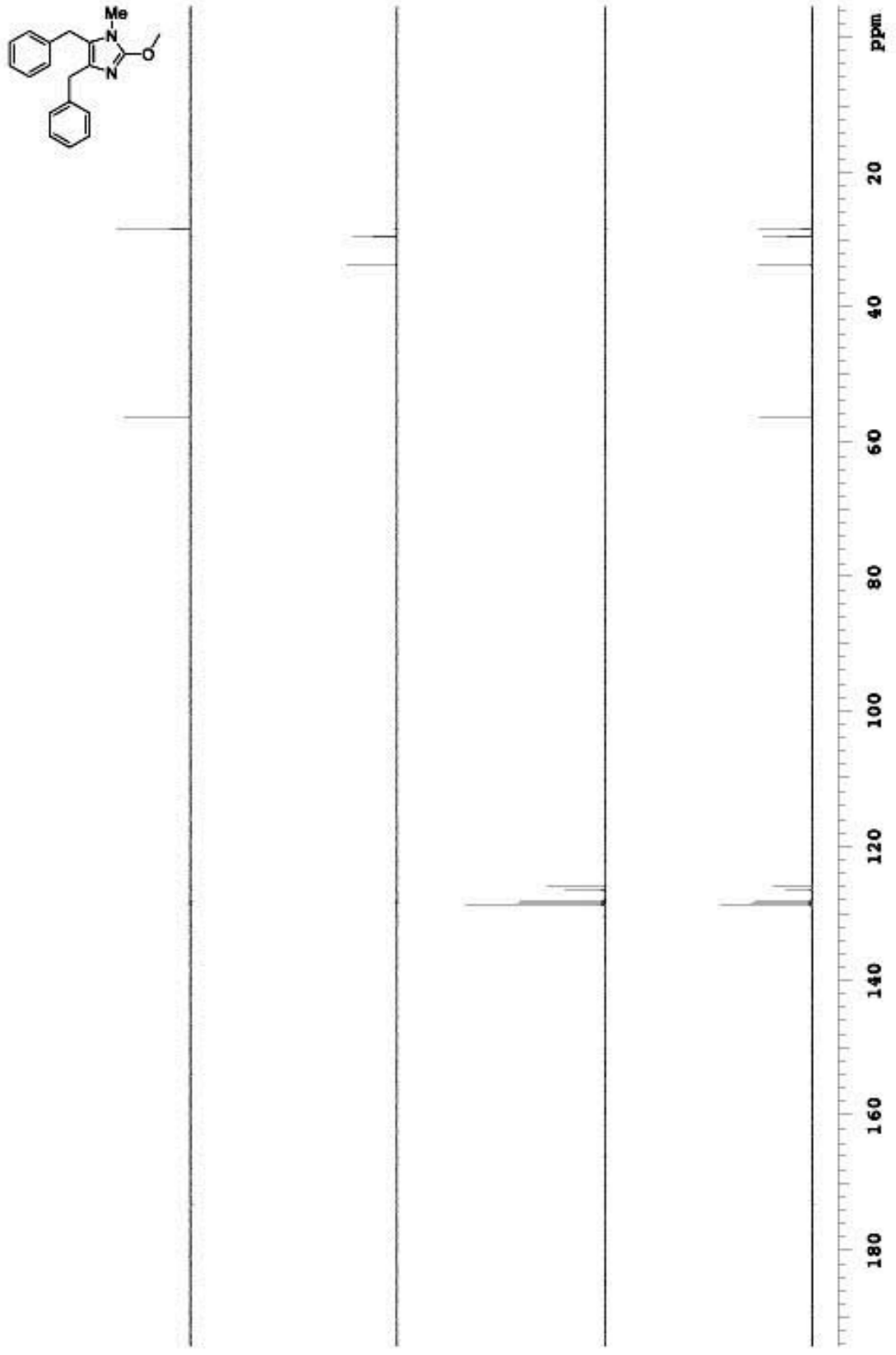
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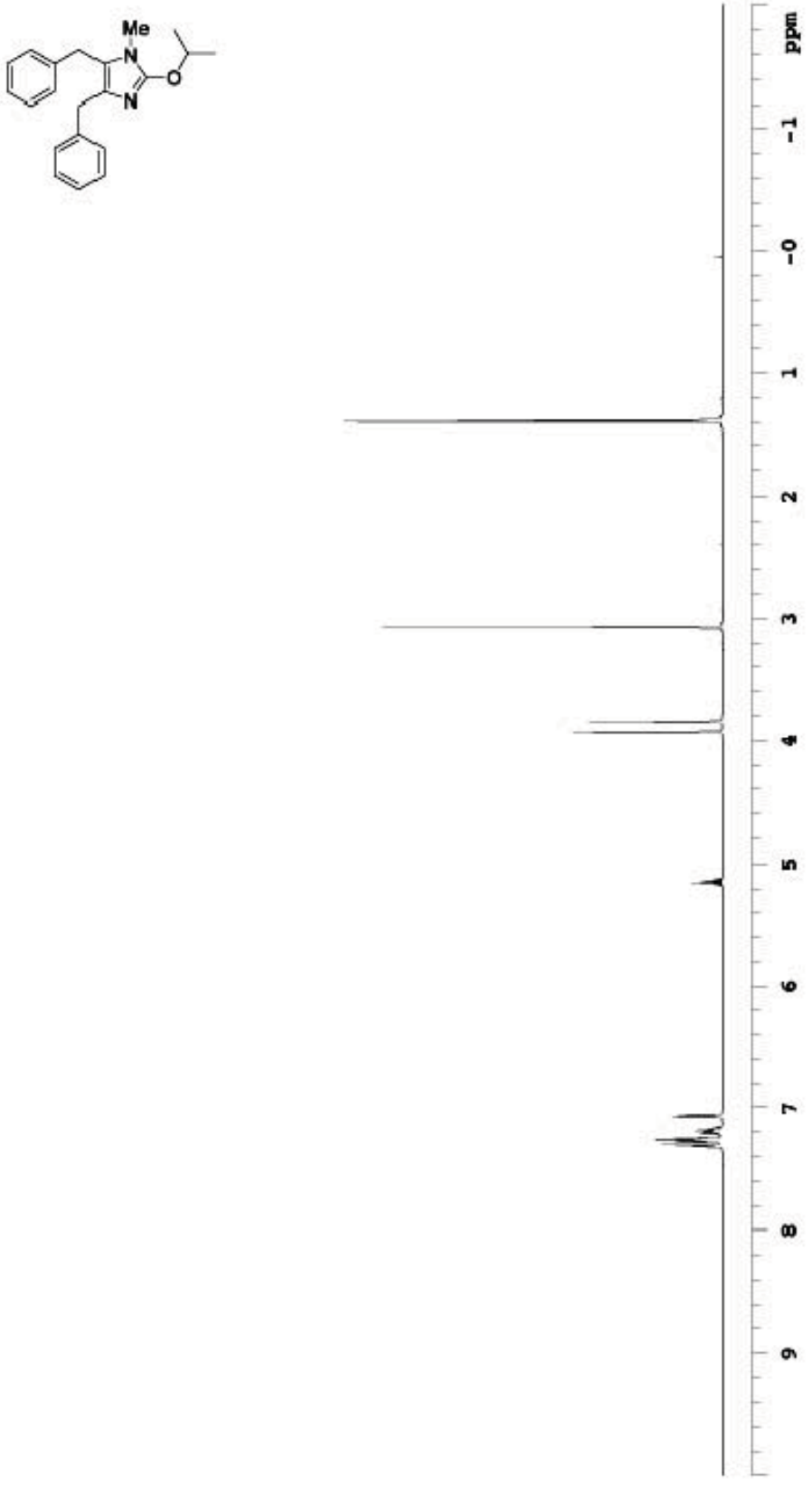
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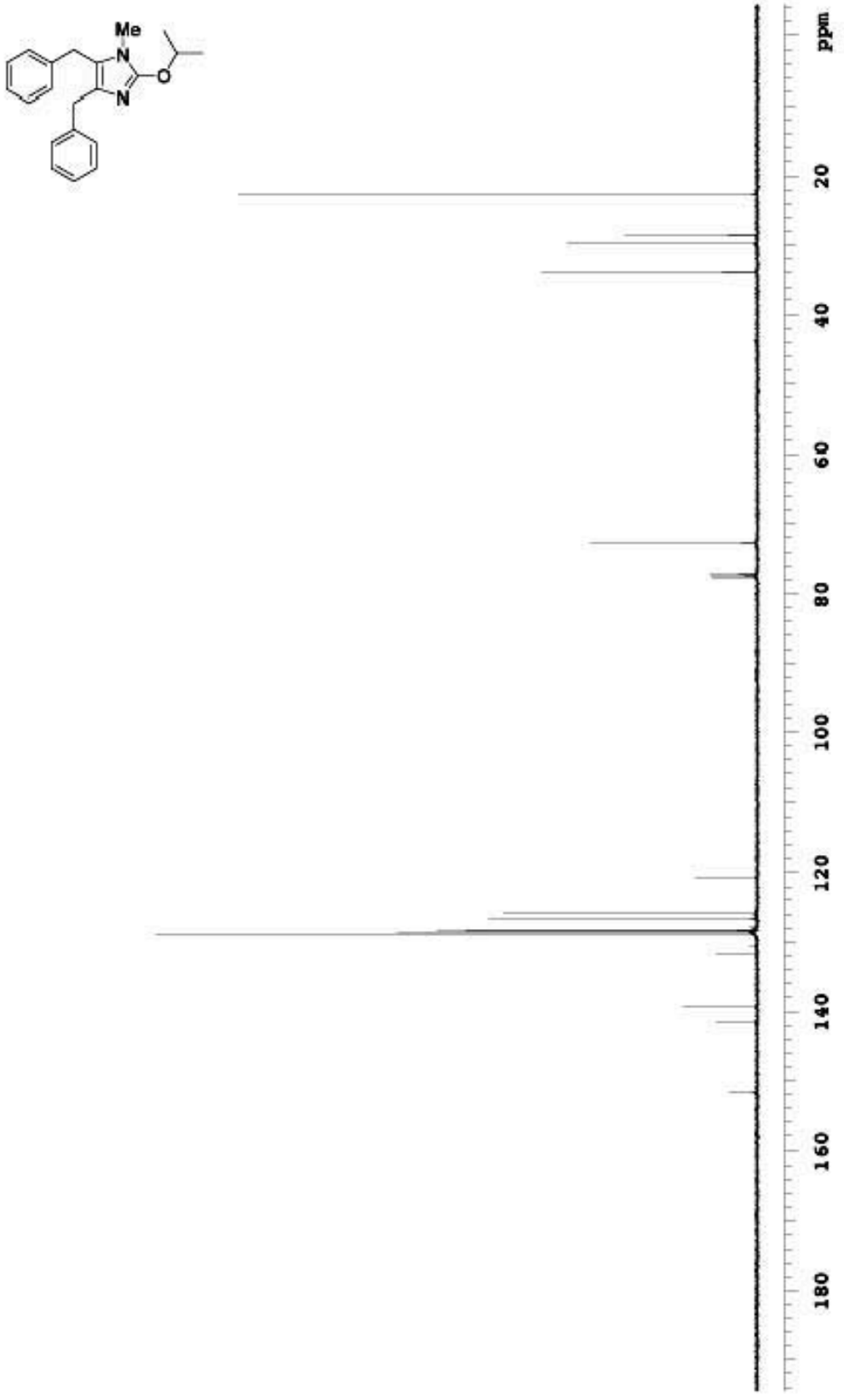
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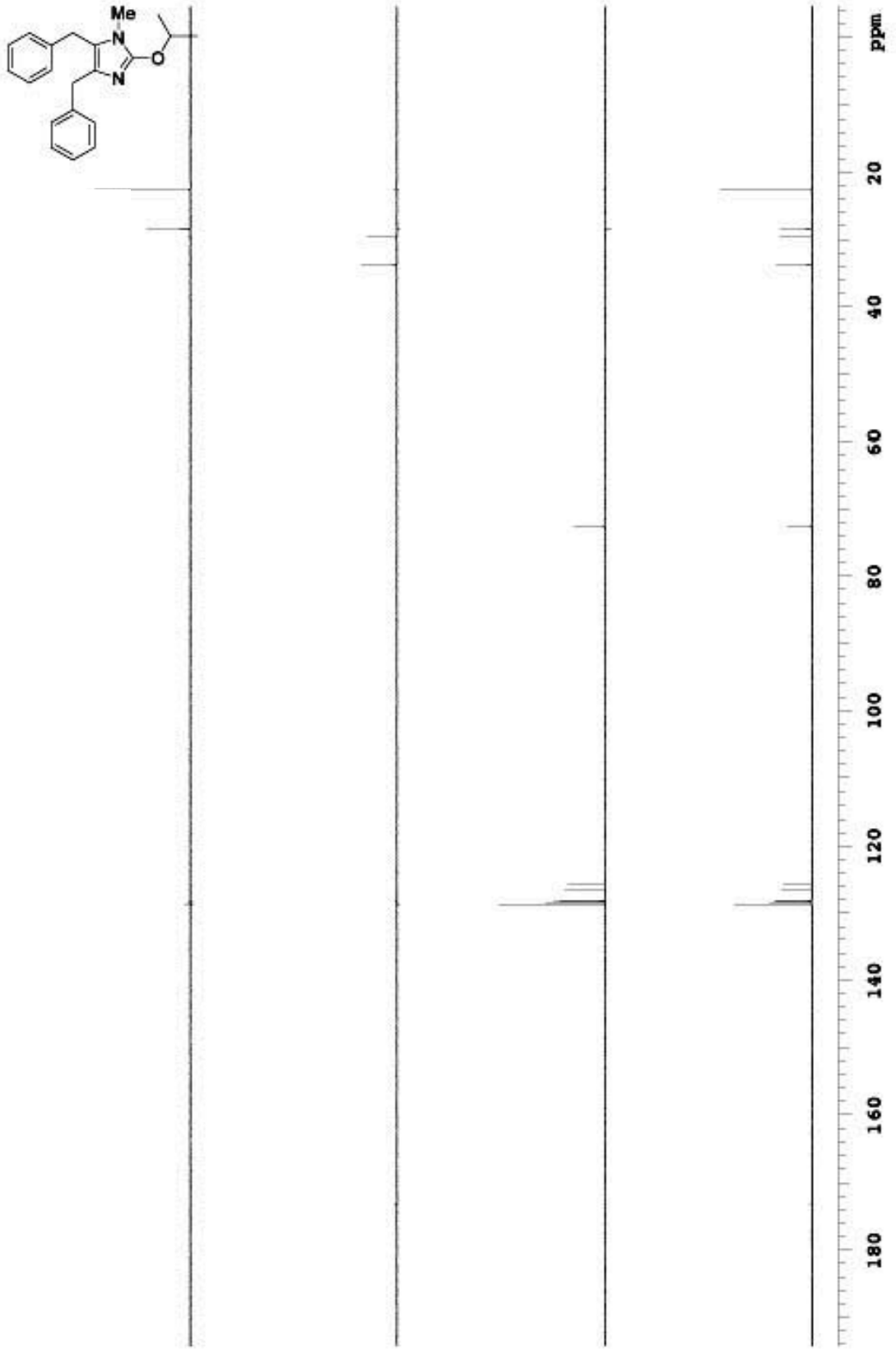
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